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=> s IgE
L1 118321 IGE

=> s l1 and epsilon constant region
L2 18 L1 AND EPSILON CONSTANT REGION

=> dup remove l2
PROCESSING COMPLETED FOR L2
L3 7 DUP REMOVE L2 (11 DUPLICATES REMOVED)

=> d l3 1-7 cbib abs

L3 ANSWER 1 OF 7 MEDLINE on STN DUPLICATE 1
2002028490 Document Number: 21061911. PubMed ID: 11044561. Molecular cloning and phylogenetic analysis of a cDNA encoding the cat (Felis domesticus) Ig **epsilon constant region**.
Weber E R; Helps C R; Foster A P; Perry A C; Gruffydd-Jones T J; Hall L; Harbour D A; Duffus W P. (Heska Corporation, 1613 Prospect Parkway, Fort Collins, CO 80525, USA.. webere@heska.com) . VETERINARY IMMUNOLOGY AND IMMUNOPATHOLOGY, (2000 Oct 31) 76 (3-4) 299-308. Journal code: 8002006. ISSN: 0165-2427. Pub. country: Netherlands. Language: English.
AB A feline splenic cDNA library was screened with a (32)P-labelled cDNA probe encoding the canine **IgE** epsilon heavy chain subunit. A cDNA sequence of 1614 nucleotides encoding the complete feline **IgE** heavy chain, as well as a portion of a variable region, was identified. A search of the GenBank database revealed an identity of 82% at the nucleotide level and 76% at the amino acid level between the feline epsilon heavy chain sequence and the canine homologue. In a separate study, feline genomic DNA, isolated from whole feline embryo cells, was subjected to PCR amplification using primers based on known partial genomic DNA sequences for the feline C epsilon gene. Following removal of an intron from the 683 bp PCR product, the coding sequence yielded an ORF of 506 bp. The DNA sequence of this PCR clone differed by a single nucleotide from the cDNA clone. This difference is silent, and therefore the proteins encoded by the two sequences are identical over the regions cloned and sequenced. Phylogenetic analysis of the constant regions of nine immunoglobulin epsilon genes revealed that the feline cDNA is most similar to the canine homologue.

L3 ANSWER 2 OF 7 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
95:263946 The Genuine Article (R) Number: QR444. SEQUENCE OF THE DOG IMMUNOGLOBULIN-ALPHA AND IMMUNOGLOBULIN-**EPSILON CONSTANT -REGION** GENES. PATEL M; SELINGER D; MARK G E; HICKEY G J; HOLLIS G F (Reprint). DUPONT MERCK PHARMACEUT CO, EXPTL STN, E 400-5207, POB 80400, WILMINGTON, DE, 19880 (Reprint); MERCK RES LABS, DEPT MOLEC & CELLULAR BIOL, RAHWAY, NJ, 07065; MERCK RES LABS, DEPT ANIM DRUG EVALUAT, RAHWAY, NJ, 07065. IMMUNOGENETICS (MAR 1995) Vol. 41, No. 5, pp. 282-286. ISSN: 0093-7711. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The immunoglobulin alpha (IGHAC) and epsilon (IGHEC) germline constant region genes were isolated from a dog liver genomic DNA library. Sequence analysis indicates that the dog IGHEC gene is encoded by four exons spread

out over 1.7 kilobases (kb). The IGHAC sequence encompasses 1.5 kb and includes all three constant region coding exons. The complete exon/intron sequence of these genes is described.

L3 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 2

95337835 Document Number: 95337835. PubMed ID: 7613209. Alternative RNA of epsilon transcripts produces mRNAs encoding two membrane and four secreted **IgE** isoforms. Saxon A; Max E E; Diaz-Sanchez D; Zhang K. (Hart and Louise Lyon Laboratory, Department of Medicine, UCLA School of Medicine 90024-1680, USA.) INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (1995 May-Jun) 107 (1-3) 45-7. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB We elucidated a series of alternatively spliced human epsilon mRNAs by employing a human epsilon-specific RT-PCR strategy. Two mRNA isoforms provide for the expression of distinct membrane **IgE** proteins, the common form of which contains a novel 56-amino-acid sequence after the last **epsilon constant-region** domain. Other mRNAs encode, in addition to the classic secreted epsilon chain, at least three novel epsilon secreted proteins that lack a transmembrane domain and possess distinctive C-terminal features. Furthermore, the expression of these epsilon mRNA isoforms is differentially regulated by stimuli such as interleukin-10, Fc epsilon RII cross-linking and aromatic hydrocarbons found in diesel exhaust.

L3 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN

1993:100155 Document No. 118:100155 Synthesis and regulation of trans-mRNA encoding the immunoglobulin .epsilon. heavy chain. Shimizu, Akira; Honjo, Tasuku (Cent. Mol. Biol. Genet., Kyoto Univ., Kyoto, 606-01, Japan). FASEB Journal, 7(1), 149-54 (English) 1993. CODEN: FAJOEC. ISSN: 0892-6638.

AB An Ig heavy-chain trans-mRNA of the .epsilon. class was detected in which the variable region of the human transgenic .mu. chain is correctly spliced to the first exon of the endogenous mouse .**epsilon**. **const**. **region**. All the endogenous isotypes that are targets of class switching have proved to be expressed as trans-mRNA. This indicates that Ig trans-mRNA synthesis is a general mechanism to express a second heavy-chain isotype with the variable region of the transgenic .mu. chain. Synthesis of .epsilon. trans-mRNA is regulated in a way similar to the trans-mRNAs of the .gamma. subclasses or class switching to .epsilon., i.e., interleukin-4 can induce the germline transcript of the .**epsilon**. **const**. **region**, but costimulation with lipopolysaccharide is necessary for .epsilon. trans-mRNA expression. The amt. of .epsilon. trans-mRNA induced is similar to that of .gamma.1 and higher than expected as judged from the rate of class switching to .epsilon.. All these data are consistent with the previous hypothesis that trans-mRNA is synthesized by a trans-splicing mechanism and that this mechanism is involved in the simultaneous multiple isotype expression of Ig in a single B lymphocyte.

L3 ANSWER 5 OF 7 MEDLINE on STN DUPLICATE 3

87059052 Document Number: 87059052. PubMed ID: 2431059. Expression of a recombinant murine **IgE** in transfected myeloma cells. Gritzmacher C A; Liu F T. JOURNAL OF IMMUNOLOGY, (1987 Jan 1) 138 (1) 324-9. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB We constructed a recombinant gene encoding an immunoglobulin (Ig) heavy chain consisting of the variable region from the phosphorylcholine (PC)-specific secreting myeloma MOPC167 and the **epsilon constant region** from SJL mice. This gene, cloned into the shuttle vector pSV2gpt, was transfected into J558L myeloma cells, and stable transformants that expressed the epsilon gene were cloned. The **IgE** heavy chain in these transformants is associated with the endogenous lambda light chain and is secreted as an intact **IgE** molecule. However, the secreted **IgE** does not bind to PC conjugated to bovine serum albumin (PC-BSA). The MOPC167 kappa chain gene

was cloned into the shuttle vector pSV2neo and was transfected into the epsilon heavy-chain transformant. Stable transformants were cloned that expressed both the epsilon heavy chain and the kappa light chain. **IgE** secreted from such a transformant was shown to bind to PC-BSA. Both types of secreted recombinant **IgE** bound to rat basophilic leukemia (RBL) cells, but only the **IgE** produced by the cell line transformed with the MOPC167 kappa gene could be cross-linked with PC-BSA to cause serotonin release.

L3 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 4

85163728 Document Number: 85163728. PubMed ID: 2580239. A hapten-specific *chimaeric **IgE** antibody with human physiological effector* function. Neuberger M S; Williams G T; Mitchell E B; Jouhal S S; Flanagan J G; Rabbitts T H. NATURE, (1985 Mar 21-27) 314 (6008) 268-70. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Immunoglobulin E (**IgE**) has a central role in allergic reactions although it rarely exceeds 5 micrograms ml-1 even in the serum of severely allergic individuals. Both mast cells and basophils possess receptors which bind the Fc portion of **IgE** with high affinity; crosslinking of membrane-bound **IgE** by allergen results in degranulation of the cell and release of a variety of pharmacologically active mediator including histamine. Myeloma **IgE** has been successfully used to block the skin sensitizing activity of allergic sera; *however, human myeloma **IgE** is clearly in limited supply.* The emergence of techniques allowing the stable introduction of immunoglobulin gene DNA into myeloma cells has allowed us to construct a mouse cell line that secretes a chimaeric **IgE**, lambda 1 antibody whose heavy chain is composed of a human C **epsilon constant region** fused to a mouse variable (VH) region. This chimaeric **IgE** is specific for the hapten 4-hydroxy-3-nitro-phenacetyl (NP) and can, when crosslinked by antigen, trigger the degranulation of human basophils. When not crosslinked, however, the chimaeric **IgE** can prevent the passive sensitization of these cells by sera from allergic subjects.

L3 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS on STN

1982:609518 *Document No. 97:209518* The sequence of a human immunoglobulin epsilon heavy chain constant region gene, and evidence for three non-allelic genes. Flanagan, John G.; Rabbitts, Terence H. (Lab. Mol. Biol., MRC, Cambridge, CB2 2QH, UK). EMBO Journal, 1(5), 655-60 (English) 1982. CODEN: EMJODG. ISSN: 0261-4189.

AB An **IgE** heavy chain gene was isolated from a DNA library of the human .epsilon. chain-producing myeloma 266B1, using a JH gene region probe. The gene was shown to be the one expressed in the myeloma by Southern hybridization anal. and by comparison of nucleotide sequences with the known amino acid sequence of the .epsilon. chain made by the myeloma. The gene consists of a variable region segment sepd. from a const. region segment by a 3.5-kilobase intervening sequence. The complete sequence of the const. region gene segment [83745-22-6] shows that this segment is split by intervening sequences into 4 coding segments corresponding to the 4 const. region domains of the protein. Using the cloned .**epsilon. const. region** gene segment as a probe, evidence was obtained from Southern hybridization anal. for 3 non-allelic .**epsilon. const. region** genes. An order on the chromosome for these 3 genes can be predicted from their pattern of retention in myeloma 266B1 DNA.

```
=> s l1 and "Cepsilon 2 domain"
L4            0 L1 AND "CEPSILON 2 DOMAIN"

=> s l1 and C2 domain
L5            8 L1 AND C2 DOMAIN
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=> dup remove l5
PROCESSING COMPLETED FOR L5
L6 4 DUP REMOVE L5 (4 DUPLICATES REMOVED)

=> d l6 1-4 cbib abs

L6 ANSWER 1 OF 4 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
2001:537843 The Genuine Article (R) Number: 446EM. Fine mapping of inhibitory anti-factor V antibodies using factor V **C2 domain** mutants - Identification of two antigenic epitopes involved in phospholipid binding. Izumi T; Kim S W; Greist A; Macedo-Ribeiro S; Fuentes-Prior P; Bode W; Kane W H; Ortel T L (Reprint). Duke Univ, Dept Med, Div Hematol, Med Ctr, Box 3422, Durham, NC 27710 USA (Reprint); Duke Univ, Dept Med, Div Hematol, Med Ctr, Durham, NC 27710 USA; Duke Univ, Dept Pathol, Div Hematol, Med Ctr, Durham, NC 27710 USA; Indiana Hemophilia & Thrombosis Ctr, Indianapolis, IN USA; Max Planck Inst Biochem, Abt Strukturforsch, D-8033 Martinsried, Germany. THROMBOSIS AND HAEMOSTASIS (JUN 2001) Vol. 85, No. 6, pp. 1048-1054. Publisher: F K SCHATTAUER VERLAG GMBH. P O BOX 10 45 43, LENZHALDE 3, D-70040 STUTTGART, GERMANY. ISSN: 0340-6245. Pub. country: USA; Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Hemorrhagic factor V inhibitors frequently bind to the second C-type (**C2**) **domain** of factor V and interfere with phospholipid binding. To define specific residues recognized by inhibitors from four patients (one bovine thrombin-induced and three spontaneous antibodies), epitope mapping was performed using recombinant human factor V lacking most of the B-type domain (FV des B) and alanine-substituted mutants within the CZ domain (FV des B C2 mutants). FV des B C2 mutants located in the region between Lys(2060) and Glu(2069) were resistant to inhibition by three IgG preparations including the bovine thrombin-induced antibody in both prothrombinase and phospholipid-binding assays. In contrast, mutations at Lys(2087) and Lys(2092)/ Glu(2096) were significantly resistant to inhibition by the fourth **Ige** preparation in both prothrombinase and phospholipid-binding assays. These results confirm interference of phospholipid binding by hemorrhagic factor V inhibitors and support the role(s) of these residues in phospholipid binding.

L6 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 1
1999404940 Document Number: 99404940. PubMed ID: 10467147. An immunoglobulin-like fold in a major plant allergen: the solution structure of Phl p 2 from timothy grass pollen. De Marino S; Morelli M A; Fraternali F; Tamborini E; Musco G; Vrtala S; Dolecek C; Arosio P; Valenta R; Pastore A. (NIMR, Mill Hill, London, UK.) STRUCTURE WITH FOLDING & DESIGN, (1999 Aug 15) 7 (8) 943-52. Journal code: 100889329. ISSN: 0969-2126. Pub. country: ENGLAND: United Kingdom. Language: English.
AB BACKGROUND: Grass pollen allergens are the most important and widespread elicitors of pollen allergy. One of the major plant allergens which millions of people worldwide are sensitized to is Phl p 2, a small protein from timothy grass pollen. Phl p 2 is representative of the large family of cross-reacting plant allergens classified as group 2/3. Recombinant Phl p 2 has been demonstrated by immunological cross-reactivity studies to be immunologically equivalent to the natural protein. RESULTS: We have solved the solution structure of recombinant Phl p 2 by means of nuclear magnetic resonance techniques. The three-dimensional structure of Phl p 2 consists of an all-beta fold with nine antiparallel beta strands that form a beta sandwich. The topology is that of an immunoglobulin-like fold with the addition of a C-terminal strand, as found in the **C2** **domain** superfamily. Lack of functional and sequence similarity with these two families, however, suggests an independent evolution of Phl p 2 and other homologous plant allergens. CONCLUSIONS: Because of the high homology with other plant allergens of groups 1 and 2/3, the structure of Phl p 2 can be used to rationalize some of the immunological properties of the whole family. On the basis of the structure, we suggest possible sites of interaction with **IgE** antibodies. Knowledge of the Phl p 2 structure may assist the rational structure-based design of

synthetic vaccines against grass pollen allergy.

L6 ANSWER 3 OF 4 MEDLINE on STN
96304316 Document Number: 96304316. PubMed ID: 8660423. Gene duplication and recombination in the evolution of mammalian Fc receptors. Hughes A L. (Department of Biology, Pennsylvania State University, University Park, PA 16802, USA.) JOURNAL OF MOLECULAR EVOLUTION, (1996 Jul) 43 (1) 4-10. Journal code: 0360051. ISSN: 0022-2844. Pub. country: United States. Language: English.

AB The immunoglobulin-related chains of cell-surface receptors for the Fc region of immunoglobulins (FcepsilonRIalpha, FcgammaRI, FcgammaRII, and FcgammaRIIIalpha) are encoded by members of a gene family. Phylogenetic analysis of representative members of this family from mammals revealed that FcgammaRIIIalpha genes of human, mouse, and rat are not orthologous to one another in the region of the gene encoding the immunoglobulin C2-set domains. In phylogenetic trees of this region, FcgammaRIIIalpha and FcgammaRII clustered together. However, in trees based on both coding and noncoding regions 5' and 3' to the **C2 domains**, FcgammaRIIIalpha genes of human, mouse, and rat clustered together. This pattern of relationship is most easily explained as a result of two independent recombinational events occurring in the mouse and rat after these two species diverged, in each of which the exons encoding the **C2 domains** were donated to an FcgammaRIIIalpha gene by an FcgammaRII gene.

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
1991:677518 Document No. 115:277518 Elucidation of the epitope locations of human autoanti-**IgE**: recognition of two epitopes located within the C.epsilon.2 and the C.epsilon.4 domains. Shakib, F.; Powell-Richards, A. (Queen's Med. Cent., Univ. Hosp., Nottingham, NG7 2UH, UK). International Archives of Allergy and Applied Immunology, 95(2-3), 102-8 (English) 1991. CODEN: IAAAAM. ISSN: 0020-5915.

AB IgG autoanti-**IgE** is detectable in a large proportion of individuals with allergic asthma, where it is suggested to be potentially involved in modulating **IgE**-mediated hypersensitivity. Using a series of overlapping recombinant human .epsilon.-chain peptides, it was shown that circulating IgG anti-**IgE** antibodies recognize at least 2 epitopes located within the C.epsilon.2 and the C.epsilon.4 domains, resp. The C.epsilon.2 recognition site is located within the C-terminal portion of the C.epsilon.2 domain (i.e. aa301-339) which is thought to contribute residues to the Fc.epsilon.RI-binding site on **IgE**. The recognition by autoanti-**IgE** of an effector function site of such pivotal importance in **IgE**-mediated hypersensitivity suggests that it plays a possible modulatory role during mast cell and basophil activation.

=> s IgE mimotope
L7 23 IGE MIMOTOPE

=> dup remove l7
PROCESSING COMPLETED FOR L7
L8 9 DUP REMOVE L7 (14 DUPLICATES REMOVED)

=> d l8 1-9 cbib abs

L8 ANSWER 1 OF 9 MEDLINE on STN DUPLICATE 1
2001639756 Document Number: 21547981. PubMed ID: 11641259. Monovalent fusion proteins of **IgE mimotop s** are safe for therapy of type I allergy. Ganglberger E; Barbara Sponer; Scholl I; Wiedermann U; Baumann S; Hafner C; Breiteneder H; Suter M; Boltz-Nitulescu G; Scheiner O; Jensen-Jarolim E. (Department of Pathophysiology, University of Vienna, A-1090 Vienna, Austria.) FASEB JOURNAL, (2001 Nov) 15 (13) 2524-6. Journal code: 8804484. ISSN: 1530-6860. Pub. country: United States. Language: English.

AB By screening phage display random peptide libraries with purified immunoglobulin E (IgE) from birch pollen-allergic patients, we previously defined peptides mimicking natural IgE epitopes (mimotopes) of the major birch pollen allergen Bet v 1. The present study aimed to define a monovalent carrier for the **IgE mimotopes** to induce protective antibodies directed to the IgE epitopes, suitable for mimotope-specific therapy. We expressed the selected mimotopes as fusion proteins together with streptococcal albumin binding protein (ABP). The fusion proteins were recognized specifically by anti-Bet v 1 human IgE, which demonstrated that the mimotopes fused to ABP resemble the natural IgE epitope. Bet v 1-specific IgG was induced by immunization of BALB/c mice with fusion proteins. These IgG antibodies could inhibit IgE binding to Bet v 1. Skin testing of Bet v 1 allergic mice showed that the ABP mimotope constructs did not elicit type I skin reactions, although they possess IgE binding structures. Our data suggest that **IgE mimotopes** are safe for epitope-specific immunotherapy of sensitized individuals, when presented in a monovalent form. Therefore, ABP-fused mimotopes are promising candidates for a new type of immunotherapy based on the precise induction of blocking antibodies.

L8 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 2
2001262396 Document Number: 21203339. PubMed ID: 11307026. **IgE mimotopes** of birch pollen allergen Bet v 1 induce blocking IgG in mice. Ganglberger E; Grunberger K; Wiedermann U; Vermes M; Sponer B; Breiteneder H; Scheiner O; Boltz G; Jensen-Jarolim E. (Department of Pathophysiology (formally Department of General and Experimental Pathology), University of Vienna, Austria.) INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (2001 Jan-Mar) 124 (1-3) 395-7. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB BACKGROUND: The induction of nonanaphylactogenic 'blocking' IgG antibodies capable of inhibiting the IgE/allergen interaction represents a favorable therapeutic concept for type I allergy. However, IgG antibodies to allergens may block or enhance specific IgE binding, depending on the recognized epitope. Taking the major birch pollen allergen Bet v 1 as a model, we developed a strategy for the precise induction of IgG antibodies of a desired epitope specificity. METHODS: Random phage display peptide libraries were applied to define peptide structures mimicking natural epitopes (mimotopes) of Bet v 1. Selections were performed with BIP 1, a murine monoclonal antibody known to enhance the IgE binding to Bet v 1, and with anti-Bet v 1 IgE purified from patients' sera. The characterized Bet v 1 mimotopes were used to localize the corresponding epitope at the surface of Bet v 1 by a computer-aided mathematical approach based on the three-dimensional structure and the chemical character of the amino acids. The Bet v 1 mimotopes were further used to immunize BALB/c mice. The specificity of the induced antibodies was tested by immunoblotting and inhibition assays. RESULTS: With the three-dimensional epitope search it became possible to localize a discontinuous IgE epitope on the surface of Bet v 1 in a substantial distance from the IgG epitope of the monoclonal antibody BIP 1. Moreover, we could demonstrate that phage displaying mimotopes are immunogenic vectors for the precise induction of epitope-specific IgG. Immunization with BIP 1 mimotopes induced IgG enhancing the IgE binding to Bet v 1, whereas immunization with **IgE mimotopes** resulted in IgG capable of blocking human IgE binding in vitro. CONCLUSION: Allergen mimotopes can be used for the induction of anti allergen IgG of desired specificity. We propose that mimotope immunotherapy based on **IgE mimotopes** generated by biopannings may represent a future concept for therapy of type I allergy.

L8 ANSWER 3 OF 9 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
2001:805862 The Genuine Article (R) Number: 478XE. Monovalent fusion proteins of immunoglobulin E mimotopes are safe for therapy of type I allergy. Ganglberger E; Sponer B; Scholl I; Wiedermann U; Baumann S; Hafner C; Breiteneder H; Suter M; Boltz-Nitulescu G; Scheiner O; Jensen-Jarolim E

(Reprint). Univ Vienna, Sch Med, Dept Pathophysiol, AKH-3Q, Wahringer Gurtel 18-20, A-1090 Vienna, Austria (Reprint); Univ Vienna, Sch Med, Dept Pathophysiol, A-1090 Vienna, Austria; Univ Zurich, Dept Virol, CH-8057 Zurich, Switzerland. FASEB JOURNAL (SEP 2001) Vol. 15, No. 11, pp. U4-U19. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA. ISSN: 0892-6638. Pub. country: Austria; Switzerland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB By screening phage display random peptide libraries with purified immunoglobulin E (IgE) from birch pollen-allergic patients, we previously defined peptides mimicking natural IgE epitopes (mimotopes) of the major birch pollen allergen Bet v 1. The present study aimed to define a monovalent carrier for the **IgE mimotopes** to induce protective antibodies directed to the IgE epitopes, suitable for mimotope-specific therapy. We expressed the selected mimotopes as fusion proteins together with streptococcal albumin binding protein (ABP). The fusion proteins were recognized specifically by anti-Bet v 1 human IgE, which demonstrated that the mimotopes fused to ABP resemble the natural IgE epitope. Bet v 1-specific IgG was induced by immunization of BALB/c mice with fusion proteins. These IgG antibodies could inhibit IgE binding to Bet v 1. Skin testing of Bet v 1 allergic mice showed that the ABP mimotope constructs did not elicit type I skin reactions, although they possess IgE binding structures. Our data suggest that **IgE mimotopes** are safe for epitope-specific immunotherapy of sensitized individuals, when presented in a monovalent form. Therefore, ABP-fused mimotopes are promising candidates for a new type of immunotherapy based on the precise induction of blocking antibodies.

L8 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
2000:608610 Document No. 133:206755 Immunogens comprising a peptide and a carrier derived from Haemophilus influenzae protein D. Coste, Michel; Lobet, Yves; Van-Mechelen, Marcelle Paulette; Verriest, Christophe (Smithkline Beecham Biologicals S.A., Belg.). PCT Int. Appl. WO 2000050077 A1 20000831, 53 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP1457 20000222. PRIORITY: GB 1999-4405 19990225; GB 1999-4408 19990225; GB 1999-4412 19990225; GB 1999-19260 19990813.

AB The present invention provides peptide immunogens linked to a carrier wherein the carrier is derived from Haemophilus Influenzae Protein D or fragments thereof. Compns comprising the antigen peptide, protein D epitope or mimotope, and immune adjuvant (e.g. saponin, aluminum salt, oil in water emulsion, or liposome) are useful for treating infection or chronic diseases.

L8 ANSWER 5 OF 9 MEDLINE on STN DUPLICATE 3
2001042128 Document Number: 20507634. PubMed ID: 11053238. Allergen mimotopes for 3-dimensional epitope search and induction of antibodies inhibiting human IgE. Ganglberger E; Grunberger K; Sponer B; Radauer C; Breiteneder H; Boltz-Nitulescu G; Scheiner O; Jensen-Jarolim E. (Department of Pathophysiology, AKH, Medical School, University of Vienna, A-1090 Vienna, Austria.) FASEB JOURNAL, (2000 Nov) 14 (14) 2177-84. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB There is no definite information available on the structural characteristics of IgE binding epitopes on allergenic molecules, although it is widely accepted that most of them are conformational. In the current study we aimed to characterize the IgE epitope of Bet v 1, the major birch pollen allergen, by the application of phage display peptide libraries. We purified IgE specific for Bet v 1 from allergic patients'

sera to select mimotopes representing artificial IgE epitopes by biopanning of phage libraries. By linear alignment, it was not possible to attribute mimotope sequences to the primary structure of Bet v 1. We developed a computer-aided, 3-dimensional coarse-grained epitope search. The 3-dimensional search, followed by statistical analysis, revealed an exposed area on the Bet v 1 molecule (located between residues 9-22 and 104-123) as the IgE binding structure. The IgE epitope was located at a 30 A distance from a previously described IgG epitope and the respective mimotope, designated Bet mim E. Such mimotopes could potentially be used for the induction of IgG capable of interfering with the IgE/allergen interaction. To test this hypothesis, we immunized BALB/c mice with the phage-displayed Bet mim E. Immunizations resulted in the induction of Bet v 1-specific IgG, which was able to block the IgE binding to Bet v 1 in vitro. Based on these observations, we propose that immunotherapy with **IgE mimotopes** generated by biopannings result in formation of blocking IgG. We conclude that mimotope immunotherapy may represent a new and promising concept for treatment of type I allergic disease.

L8 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN

2000:53752 Document No. 132:346309 Regulation of immunoglobulin E inflammation: Anti-immunoglobulin E autoantibodies. Stadler, Beda M.; Vogel, Monique; Miescher, Sylvia Margaret; Zuercher, Adrian Walter; Rudolf, Michael P.; Kricek, Franz (University of Bern, Bern, Switz.). Lung Biology in Health and Disease, 136(Immunotherapy in Asthma), 431-438 (English) 1999. CODEN: LBHDD7. ISSN: 0362-3181. Publisher: Marcel Dekker, Inc..

AB A review with 43 refs. Discussed are: anti-IgE autoantibodies (occurrence; in vitro models for anti-IgE activity; isolation of anti-IgE autoantibodies by repertoire cloning); mimicry of IgE epitopes (epitope specificity and biol. activity of anti-IgE antibodies; **IgE mimotopes**); anti-idiotypic antibodies as epitope mimicry; and therapeutic strategies based on anti-IgE antibodies (passive immunization with humanized antibodies; active immunization).

L8 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN

1998:612276 Document No. 129:289101 A mimotope defined by phage display inhibits IgE binding to the plant panallergen profilin. Leitner, Agnes; Vogel, Monique; Radauer, Christian; Breiteneder, Heimo; Stadler, Beda M.; Scheiner, Otto; Kraft, Dietrich; Jensen-Jarolim, Erika (Department General Experimental Pathology, University Vienna, Vienna, A-1090, Austria). European Journal of Immunology, 28(9), 2921-2927 (English) 1998. CODEN: EJIMAF. ISSN: 0014-2980. Publisher: Wiley-VCH Verlag GmbH.

AB Birch pollen and mugwort pollen allergies are often assocd. with hypersensitivity to plant foods. This clin. and serol. cross-reactivity is mediated by IgE antibodies reacting with homologous proteins in pollen and food. Cross-reacting homologs of the important birch pollen allergen Bet v 2 (profilin) were detected in other pollen, fruits, nuts, and vegetables, such as celery tuber. The authors purified IgG/IgE antibodies from the serum of an exclusively profilin-allergic patient using affinity columns either coupled with protein exts. from mugwort pollen, birch pollen, or celery tuber. Constrained and unconstrained random nonapeptide libraries were pooled and screened with the anti-profilin antibody prepns. to define cross-reactive ligands. Specific ligands were enriched by successive panning rounds using the profilin-specific antibodies in series. After the last panning round enriched phage clones were screened with purified profilin-specific antibodies and IgE-binding clones were sequenced. Five of 8 pos. clones (62.5%) displayed the same circular peptide CAISGGYPVC. This peptide was synthesized and examd. for its ability to inhibit IgE binding to blotted mugwort pollen, birch pollen, or celery tuber profilin. Inhibition studies showed redn. of IgE binding to profilins in all 3 protein exts. As the sequence of the mimotope did not show any homol. to the known birch profilin sequence this peptide is considered to mimic a common conformational IgE epitope for these examd. profilins.

L8 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
1998:145086 Document No. 128:242665 Anti-IgE vaccination. Stadler, Beda M.; Vogel, Monique; Rudolf, Michael; Miescher, Sylvia; Zurcher, Adrian; Kricek, Franz (Institute of Immunology and Allergology, University of Bern, Bern, Switz.). Progress in Allergy and Clinical Immunology, Proceedings of the International Congress of Allergology and Clinical Immunology, 16th, Cancun, Mex., Oct. 19-24, 1997, 339-342. Editor(s): Oehling, Albert K.; Huerta Lopez, J. G. Hogrefe & Huber: Seattle, Wash. (English) 1997. CODEN: 65SQAB.

AB A review with 34 refs. The phage display technol. has provided a new way to dissect the natural anti-IgE response. Based on the authors' results, the question can now be addressed whether it may be possible to redirect a human anti-IgE response by active immunization with **IgE-mimotopes** or anti-idiotypic antibodies. To understand allergic disease, it can also be envisaged that a radical approach to eliminate or neutralize IgE will finally be the proof of how important the IgE mol. is for the pathophysiol. of the IgE mediated diseases.

L8 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 4
97276834 Document Number: 97276834. PubMed ID: 9130527. Can active immunization redirect an anti-IgE immune response?. Stadler B M; Rudolf M P; Vogel M; Miescher S; Zurcher A W; Kricek F. (Institute of Immunology and Allergology, Inselspital, Bern, Switzerland.. stadler@insel.unibe.ch) . INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (1997 May-Jul) 113 (1-3) 216-8. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB We used as a template a mouse monoclonal antibody against IgE to isolate peptides from random peptide phage display libraries. Thereby, two types of peptides were isolated that corresponded to two different epitopes on the human IgE molecule. These peptides, also called mimotopes, seem to be a suitable tool in conjunction with carriers to induce an autoimmune response with a beneficial effect in humans, because the originally used template antibody is capable of neutralizing IgE, is nonanaphylactogenic, and inhibits IgE synthesis. The vaccination approach is further supported by the fact that we were capable of isolating anti-idiotypic antibodies from antibody phage display libraries against the template antibody. These anti-idiotypic antibodies were inhibited by both of the isolated **IgE mimotopes**. Thus, active vaccination with defined **IgE mimotopes** may represent a follow-up drug for the presently used anti-IgE antibodies.

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L9 0 L1 AND SURFACE EPOSED EPITOPE

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L10 6 L1 AND SURFACE EXPOSED EPITOPE

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L11 ANSWER 1 OF 2 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
95:826288 The Genuine Article (R) Number: TF776. SEROLOGIC EVIDENCE FOR A CLASS-I GROUP-A STREPTOCOCCAL INFECTION AMONG RHEUMATIC-FEVER PATIENTS. BESSEN D E (Reprint); VEASY L G; HILL H R; AUGUSTINE N H; FISCHETTI V A. YALE UNIV, SCH MED, EPIDEMIOL & PUBL HLTH LAB, 333 CEDAR ST, NEW HAVEN, CT, 06520 (Reprint); YALE UNIV, SCH MED, DEPT EPIDEMIOL & PUBL HLTH, MICROBIOL SECT, NEW HAVEN, CT, 06520; UNIV UTAH, SCH MED, DEPT PEDIAT, SALT LAKE CITY, UT, 00000; UNIV UTAH, SCH MED, DEPT PATHOL, SALT LAKE CITY, UT, 00000; ROCKEFELLER UNIV, BACTERIAL PATHOGENESIS & IMMUNOL, NEW YORK, NY, 10021. JOURNAL OF INFECTIOUS DISEASES (DEC 1995) Vol. 172, No.

6, pp. 1608-1611. ISSN: 0022-1899. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Group A streptococci (GAS) of serotypes most commonly associated with rheumatic fever (RF) outbreaks differ from many other serotypes by the presence of a unique, **surface-exposed epitope** on the M protein molecule, Based on the presence or absence of this epitope, GAS are categorized as class I or II, respectively, The objective of this study was to determine whether RF patients have an altered immune response to the class I-specific epitope, Immunoreactivity to class I- and class II-specific epitopes was determined for serum IgG derived from persons with a recent history of acute RF, uncomplicated GAS pharyngitis, and no known recent GAS infection. The results indicate that only RF patients display elevated levels of serum **Ige** directed towards the class I-specific epitope; they lack immunoreactivity to the class II epitope, The serologic findings strongly suggest that many of the RF patients were recently infected with a class I GAS isolate.

L11 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1

93271708 Document Number: 93271708. PubMed ID: 7684629. Studies on the allergenicity of the amino-terminal epitope (Bet v I 23-38) from birch pollen allergen. Vik H; Steinvag S K; Elsayed S. (Allergy Research Group, University Hospital, University of Bergen, Norway.) INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (1993) 101 (1) 89-94. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB An N-terminal peptide of the major allergen of birch (Bet v I 23-38) was selected for studying the activity of this segment on the basis of optimal hydrophilicity as it was tentatively suggested to be a **surface exposed epitope**. In addition two control peptides in the region 1-38 were similarly used for comparative assignment of the allergenicity. Peptide analogues from the amino acid terminal region, amino acid residues No. 23-38 of Bet v I, were synthesized by semiautomatic solid-phase peptide synthesis. In vitro and in vivo biological activity studies were performed on these analogous peptides. The **IgE**-binding capacity of the synthetic peptide 23-38 was examined using the following tests: specific **IgE** inhibition, skin prick test, nasal provocation and Prausnitz-Kustner inhibition. The results of these investigations suggested that the region 23-38 from the birch and hazel major allergen encompassed a single haptenic epitope.

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L12           0 SURFACE EXPOSED IGE DOMAIN

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L13          29 SURFACE EXPOSED AND IGE

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PROCESSING COMPLETED FOR L13
L14          11 DUP REMOVE L13 (18 DUPLICATES REMOVED)

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L14 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN

2002:391881 Document No. 136:400602 Mutant allergens with reduced **IgE** binding affinity and improved safety for specific allergy vaccination. Holm, Jens; Ipsen, Henrik; Nedergaard Larsen, Jorgen; Spangfort, Michael Dho (Alk-Abello A/S, Den.). PCT Int. Appl. WO 2002040676 A2 20020523, 210 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,

TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-DK764 20011116. PRIORITY: DK 2000-1718 20001116; US 2000-PV249361 20001116; US 2001-PV298170 20010614.

AB Novel recombinant allergens with multiple mutations and reduced **IgE** binding affinity are disclosed. The allergens are non-naturally occurring mutants of naturally-occurring allergens, including birch pollen Bet v 1 of Betula verrucosa, wasp venom Ves v 5 from Vespula vulgaris, house dust mite Der p 1 and Der p 2 from Dermatophagoides farinae and D. pteronyssinus, resp., and grass Phl p 5 from Phleum pratense. Site-directed mutagenesis and DNA shuffling is used to replace **surface exposed** residues of the allergens while the overall .alpha.-carbon backbone tertiary structure is essentially preserved. The inventive idea of the present idea is based on the recognition that a mutated allergen having **IgE** binding reducing mutations in multiple B cell epitopes, and at least one intact epitope, would on the one hand reduce the allergen-mediated crosslinking and on the other hand allow the raising of an IgG response with a binding ability competitive with that of **IgE**. The mutant allergen constitutes a highly advantageous allergen in that the risk of anaphylactic reactions is strongly reduced. X-ray crystallog. anal. of the three-dimensional structure is used to identify **surface-exposed** amino acid residues, and the retention of .alpha.-carbon backbone tertiary structure. Vaccination efficiency is measured by **IgE** binding, T cell proliferation assay, histamine release assays with human basophil, T cell reactivity based on proliferation and cytokine prodn., and induction of IgG antibodies and blocking antibodies.

L14 ANSWER 2 OF 11 MEDLINE on STN DUPLICATE 1

2001160983 Document Number: 21135826. PubMed ID: 11240953.

Cross-reactivity studies of a new group 2 allergen from the dust mite Glycyphagus domesticus, Gly d 2, and group 2 allergens from Dermatophagoides pteronyssinus, Lepidoglyphus destructor, and Tyrophagus putrescentiae with recombinant allergens. Gafvelin G; Johansson E; Lundin A; Smith A M; Chapman M D; Benjamin D C; Derewenda U; van Hage-Hamsten M. (Department of Medicine, Division of Clinical Immunology and Allergy, Karolinska Hospital and Institutet, Stockholm, Sweden.) JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (2001 Mar) 107 (3) 511-8. Journal code: 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Dust mites are important inducers of allergic disease. Group 2 allergens are recognized as major allergens in several mite species, including Dermatophagoides pteronyssinus, Lepidoglyphus destructor, and Tyrophagus putrescentiae. No allergens have thus far been characterized on the molecular level from the dust mite Glycyphagus domesticus. OBJECTIVE: We sought to examine the cross-reactivity among group 2 allergens of G domesticus, L destructor, T putrescentiae, and D pteronyssinus. METHODS: A group 2 allergen from G domesticus, Gly d 2, was cloned and expressed as a recombinant protein. Cross-reactivity between Gly d 2 and 3 other group 2 allergens, Lep d 2, Tyr p 2, and Der p 2, was studied by using individual sera and a serum pool RAST-positive to G domesticus, L destructor, T putrescentiae, and D pteronyssinus. Recombinant allergens were used as inhibitors of **IgE** binding in immunoblotting experiments. Molecular modeling on the basis of the Der p 2 structure was carried out for Gly d 2, Lep d 2, and Tyr p 2. RESULTS: Two cDNAs encoding isoforms of Gly d 2 were isolated, but only the Gly d 2.02 isoform was used in this study. Sixteen of 17 subjects had **IgE** to Gly d 2. The protein sequence of Gly d 2 revealed 79% identity to Lep d 2 and 46% and 41% identity to Tyr p 2 and Der p 2, respectively. Extensive cross-reactivity was demonstrated among Gly d 2, Lep d 2, and Tyr p 2, but little cross-reactivity was found between these allergens and Der p 2. According to the tertiary structure of Der p 2 and 3-dimensional models of Gly d 2, Lep d 2, and Tyr p 2, differences reside mainly in **surface-exposed** residues. CONCLUSION: Gly d 2 showed high sequence homology to Lep d 2. Cross-reactivity was observed between Gly d 2, Lep d 2, and Tyr p 2, but only limited cross-reactivity was demonstrated between these 3 allergens and Der p 2.

L14 ANSWER 3 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2
2001:233526 Document No.: PREV200100233526. Nonallergenic peptides from **surface-exposed** areas or B-cell epitopes of allergens for specific immunotherapy. Focke, M.; Mahler, V.; Ball, T.; Kraft, D.; Valenta, R. [Reprint author]. Molecular Immunopathology Group, Department of Pathophysiology, AKH, University of Vienna, Waehringer Guertel 18-20, A-1090, Vienna, Austria. rudolf.valenta@akh-wien.ac.at. International Archives of Allergy and Immunology, (January-March, 2001) Vol. 124, No. 1-3, pp. 398-399. print.
CODEN: IAAIEG. ISSN: 1018-2438. Language: English.

L14 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
2000:608780 Document No. 133:206771 Epitopes or mimotopes derived from the C.epsilon.2 domain of **IgE**, antagonists thereof, and their therapeutic uses. Dyson, Michael; Friede, Martin; Greenwood, Judith; Hewitt, Ellen; Lamont, Alan; Mason, Sean; Randall, Roger; Turnell, William Gordon; Van Mechelen, Marcelle Paulette; Vinals y De Bassols, Carlota (Smithkline Beecham Biologicals S.A., Belg.; Peptide Therapeutics Limited). PCT Int. Appl. WO 2000050460 A1 20000831, 129 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English).
CODEN: PIXXD2. APPLICATION: WO 2000-EP1455 20000222. PRIORITY: GB 1999-4405 19990225; GB 1999-7151 19990329; GB 1999-10537 19990507; GB 1999-10538 19990507; GB 1999-18594 19990807; GB 1999-18603 19990807; GB 1999-21046 19990907; GB 1999-21047 19990907; GB 1999-25619 19991029; GB 1999-27698 19991123.
AB The present invention relates to the provision of novel medicaments for the treatment, prevention or amelioration of allergic disease. In particular, the novel medicaments are isolated peptides incorporating epitopes or mimotopes of ***surface exposed*** regions of the C<e2 domain of **IgE**. The inventors have found that these novel regions may be the target for both passive and active immunoprophylaxis or immunotherapy. The invention further relates to methods for prodn. of the medicaments, pharmaceutical compns. contg. them and their use in medicine. Also forming an aspect of the present invention are ligands, esp. monoclonal antibodies, which are capable of binding the ***surface exposed IgE*** regions of the present invention, and their use in medicine as passive immunotherapy or in immunoprophylaxis.

L14 ANSWER 5 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
1999:129223 Document No.: PREV199900129223. Molecular structure of the major birch allergen and the effect of ***surface exposed*** amino acid substitution on **IgE** binding. Larsen, J. N. [Reprint author]; Gajhede, M.; Ipsen, H. [Reprint author]; Spangfort, M. D. [Reprint author]; Van Neerven, R. J. J. [Reprint author]; Schou, C. [Reprint author]; Lowenstein, H. [Reprint author]. Alk-Abello, Horsholm, Denmark. European Respiratory Journal, (Sept., 1998) Vol. 12, No. SUPPL. 28, pp. 275S. print.
Meeting Info.: European Respiratory Society Annual Congress. Geneva, Switzerland. September 19-23, 1998. The European Respiratory Society.
CODEN: ERJOEI. ISSN: 0903-1936. Language: English.

L14 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2003 ACS on STN
1997:474624 Document No. 127:175343 Reduction of **IgE** antibody binding to rDer p 2 variants generated by site-directed mutagenesis. Smith, Alisa M.; Chapman, Martin D. (Asthma and Allergic Diseases Center, Department of Medicine, University of Virginia, Charlottesville, VA,

22908, USA). Advances in Experimental Medicine and Biology, 409(New Horizons in Allergy Immunotherapy), 391-394 (English) 1996. CODEN: AEMBAP. ISSN: 0065-2598. Publisher: Plenum.

AB Here, the authors demonstrate the contribution of 3 disulfide bonds of Der p 2 to the antigenic structure of the protein. In addn., the bonds make different contributions to maintaining this structure. Residues predicted to be **surface exposed** are involved in epitopes defined by monoclonal antibodies, but variants at these positions did not distinguish a population of **IgE** antibody epitopes. Variants with reduced **IgE** binding may provide an alternative strategy for immunotherapy. The use of complete recombinant proteins with reduced **IgE** binding, but with a full complement of T cell epitopes, may offer an alternative approach to immunotherapy, which could potentially be applicable to any cloned allergen.

L14 ANSWER 7 OF 11 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

95:826288 The Genuine Article (R) Number: TF776. SEROLOGIC EVIDENCE FOR A CLASS-I GROUP-A STREPTOCOCCAL INFECTION AMONG RHEUMATIC-FEVER PATIENTS. BESSEN D E (Reprint); VEASY L G; HILL H R; AUGUSTINE N H; FISCHETTI V A. YALE UNIV, SCH MED, EPIDEMIOL & PUBL HLTH LAB, 333 CEDAR ST, NEW HAVEN, CT, 06520 (Reprint); YALE UNIV, SCH MED, DEPT EPIDEMIOL & PUBL HLTH, MICROBIOL SECT, NEW HAVEN, CT, 06520; UNIV UTAH, SCH MED, DEPT PEDIAT, SALT LAKE CITY, UT, 00000; UNIV UTAH, SCH MED, DEPT PATHOL, SALT LAKE CITY, UT, 00000; ROCKEFELLER UNIV, BACTERIAL PATHOGENESIS & IMMUNOL, NEW YORK, NY, 10021. JOURNAL OF INFECTIOUS DISEASES (DEC 1995) Vol. 172, No. 6, pp. 1608-1611. ISSN: 0022-1899. Pub. country: USA. Language: ENGLISH. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Group A streptococci (GAS) of serotypes most commonly associated with rheumatic fever (RF) outbreaks differ from many other serotypes by the presence of a unique, **surface-exposed** epitope on the M protein molecule, Based on the presence or absence of this epitope, GAS are categorized as class I or II, respectively, The objective of this study was to determine whether RF patients have an altered immune response to the class I-specific epitope, Immunoreactivity to class I- and class II-specific epitopes was determined for serum IgG derived from persons with a recent history of acute RF, uncomplicated GAS pharyngitis, and no known recent GAS infection. The results indicate that only RF patients display elevated levels of serum **Ige** directed towards the class I-specific epitope; they lack immunoreactivity to the class II epitope, The serologic findings strongly suggest that many of the RF patients were recently infected with a class I GAS isolate.

L14 ANSWER 8 OF 11 MEDLINE on STN DUPLICATE 3

93271708 Document Number: 93271708. PubMed ID: 7684629. Studies on the allergenicity of the amino-terminal epitope (Bet v I 23-38) from birch pollen allergen. Vik H; Steinvag S K; Elsayed S. (Allergy Research Group, University Hospital, University of Bergen, Norway.) INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (1993) 101 (1) 89-94. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB An N-terminal peptide of the major allergen of birch (Bet v I 23-38) was selected for studying the activity of this segment on the basis of optimal hydrophilicity as it was tentatively suggested to be a **surface xposed** epitope. In addition two control peptides in the region 1-38 were similarly used for comparative assignment of the allergenicity. Peptide analogues from the amino acid terminal region, amino acid residues No. 23-38 of Bet v I, were synthesized by semiautomatic solid-phase peptide synthesis. In vitro and in vivo biological activity studies were performed on these analogous peptides. The **IgE**-binding capacity of the synthetic peptide 23-38 was examined using the following tests: specific **IgE** inhibition, skin prick test, nasal provocation and Prausnitz-Kustner inhibition. The results of these investigations suggested that the region 23-38 from the birch and hazel major allergen encompassed a single haptenic epitope.

L14 ANSWER 9 OF 11 MEDLINE on STN DUPLICATE 4

90060198 Document Number: 90060198. PubMed ID: 2531089. Isolation and characterization of **IgE** receptors from rat intestinal mucosal mast cells. Swieter M; Chan B M; Rimmer C; McNeill K; Froese A; Befus D. (Department of Microbiology and Infectious Diseases, University of Calgary, Alberta, Canada.) EUROPEAN JOURNAL OF IMMUNOLOGY, (1989 Oct) 19 (10) 1879-85. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.

AB High-(Fc epsilon RI) and low-(Fc epsilon RII) affinity **IgE** receptors were isolated from surface radioiodinated, Nonidet-P40-solubilized rat intestinal mucosal mast cells (IMMC) and compared with those on rat peritoneal mast cells (PMC) and rat basophilic leukemia (RBL) cells. Fc epsilon RII were isolated by affinity chromatography using **IgE**-Sepharose or by anti-Fc epsilon RII antisera and protein A-Sepharose. The **surface-exposed**, **IgE** -binding alpha subunits of Fc epsilon RI [Fc epsilon RI alpha] were isolated by affinity chromatography using **IgE** and anti-**IgE**-Sepharose. Fc epsilon RI alpha on IMMC had an apparent molecular mass of 59 kDa, somewhat larger than that of PMC (51 kDa), RBL-2H3 cells (51 kDa) or RBL-CA10.7 cells (46 kDa). Brief (45 s) incubation of IMMC or PMC in glycine-HCl, pH 3, prior to iodination removed much of the surface-bound **IgE**. This permitted more thorough labeling of the receptors, but had no affect on the estimate of receptor size. Surprisingly and in contrast to acid-treated PMC, upon anti-**IgE**-Sepharose isolation acid-treated IMMC yielded an intensely radioactive Fc epsilon RI alpha band in the absence of added **IgE**. Such a finding suggests that IMMC, more so than PMC, may have an intracellular store of **IgE**, as has been suggested by many others. IMMC also differed from PMC in the number of forms of Fc epsilon RII isolated; 50-kDa and 58-kDa forms of Fc epsilon RII were obtained from IMMC, whereas PMC yielded most often a single 56-kDa Fc epsilon RII band. These results were mimicked by the two RBL cell sublines: RBL-2H3 cells yielded two Fc epsilon RII (46 kDa and 55 kDa), but only one form of Fc epsilon RII (54-kDa) was obtained from RBL-CA10.7 cells. Thus, the two subtypes of rat mast cells, which have previously been shown to differ in mediator profile and responsiveness to secretagogues and antiallergic drugs, are also distinguished by differences in IgER profile.

L14 ANSWER 10 OF 11 MEDLINE on STN DUPLICATE 5

83221538 Document Number: 83221538. PubMed ID: 6190168. Selective phosphorylation of the **IgE** receptor in antigen-stimulated rat mast cells. Hempstead B L; Parker C W; Kulczycki A Jr. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1983 May) 80 (10) 3050-3. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Purified rat serosal mast cells were sensitized with mouse immunoglobulin E (**IgE**) anti-2,4-dinitrophenyl antibody, partially depleted of phosphate, labeled with [32P]orthophosphate, and stimulated with dinitrophenylated bovine serum albumin or control protein. After 15-120 seconds at 37 degrees C, the cells were extracted with nonionic detergent. **IgE** receptors were purified by repetitive affinity chromatography and were analyzed by NaDodSO4/polyacrylamide gel electrophoresis and radioautography. Antigenic stimulation of intact rat mast cells produced a rapid and marked increase in the phosphorylation of the **surface-exposed** alpha component of the **IgE** receptor. However, phosphorylation of the 33,000 Mr beta component of the **IgE** receptor was not altered significantly by antigen stimulation. This suggests that the selective increase in phosphorylation of the **IgE** receptor alpha component may be part of the physiologic mediator secretion process triggered by antigen.

L14 ANSWER 11 OF 11 MEDLINE on STN DUPLICATE 6

82054181 Document Number: 82054181. PubMed ID: 7299127. Characterization of the **IgE** receptor by tryptic mapping. Pecoud A R; Conrad D H. JOURNAL OF IMMUNOLOGY, (1981 Dec) 127 (6) 2208-14. Journal code:

2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB **IgE** receptors were labeled by lactoperoxidase-catalyzed surface radioiodination of rat basophilic leukemia (RBL) cells and rat peritoneal mast cells (RMC). After nonionic detergent solubilization and incubation with rat **IgE**, **IgE**-receptor complexes were immunoprecipitated using anti-rat **IgE**. The receptor for **IgE** was further purified by SDS-PAGE, the receptor peak, in the gel, was submitted to tryptic digestion, and the resulting peptides were analyzed by a 2-dimensional peptide mapping procedure. The peptides were then visualized by autoradiography. **IgE** receptors from different RBL cell lines exhibit slight differences in m.w., as judged by SDS-PAGE; however, no differences were seen in the tryptic peptide maps of receptors from the different RBL cell lines. In addition, receptors isolated from RMC also mapped identically, indicating that peptides responsible for the m.w. differences may not be labeled. The **IgE** -binding component of higher m.w., isolated by affinity chromatography on **IgE**-Sepharose, gave a distinct pattern of tryptic peptides that were different from the receptor. By using **IgE**-Sepharose and tryptic mapping, this 2nd and **IgE**-binding component was found on all RBL cell lines and on RMC. The membrane orientation of the receptor was analyzed by tryptic mapping. Tryptic maps obtained from **IgE** receptors labeled on intact cells (outside labeled only), membrane particles (inside and outside labeled), and in a detergent-solubilized form (all possible sites labeled) were similar, indicating that no other protein site was available to be labeled, in addition to those in the **surface exposed** binding site. Moreover, saturation of the receptor by **IgE** prevented its subsequent radioiodination, whether the receptor was labeled on intact cells, on membrane particles, or in a solubilized form, again indicating that no site other than the binding site could be labeled. Cumulatively, these data suggest that the **IgE** receptor on RBL cells is not a transmembrane protein.

```
=> s IgE mimotope
L15         23 IGE MIMOTOPE

=> dup remove l15
PROCESSING COMPLETED FOR L15
L16          9 DUP REMOVE L15 (14 DUPLICATES REMOVED)

=> d l16 1-9 cbib abs
```

L16 ANSWER 1 OF 9 MEDLINE on STN DUPLICATE 1

2001639756 Document Number: 21547981. PubMed ID: 11641259. Monovalent fusion proteins of **IgE mimotopes** are safe for therapy of type I allergy. Ganglberger E; Barbara Sponer; Scholl I; Wiedermann U; Baumann S; Hafner C; Breiteneder H; Suter M; Boltz-Nitulescu G; Scheiner O; Jensen-Jarolim E. (Department of Pathophysiology, University of Vienna, A-1090 Vienna, Austria.) FASEB JOURNAL, (2001 Nov) 15 (13) 2524-6. Journal code: 8804484. ISSN: 1530-6860. Pub. country: United States. Language: English.

AB By screening phage display random peptide libraries with purified immunoglobulin E (IgE) from birch pollen-allergic patients, we previously defined peptides mimicking natural IgE epitopes (mimotopes) of the major birch pollen allergen Bet v 1. The present study aimed to define a monovalent carrier for the **IgE mimotopes** to induce protective antibodies directed to the IgE epitopes, suitable for mimotope-specific therapy. We expressed the selected mimotopes as fusion proteins together with streptococcal albumin binding protein (ABP). The fusion proteins were recognized specifically by anti-Bet v 1 human IgE, which demonstrated that the mimotopes fused to ABP resemble the natural IgE epitope. Bet v 1-specific IgG was induced by immunization of BALB/c mice with fusion proteins. These IgG antibodies could inhibit IgE binding to Bet v 1. Skin testing of Bet v 1 allergic mice showed that the ABP mimotope constructs did not elicit type I skin reactions, although they

possess IgE binding structures. Our data suggest that **IgE mimotopes** are safe for epitope-specific immunotherapy of sensitized individuals, when presented in a monovalent form. Therefore, ABP-fused mimotopes are promising candidates for a new type of immunotherapy based on the precise induction of blocking antibodies.

L16 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 2
2001262396 Document Number: 21203339. PubMed ID: 11307026. **IgE mimotopes** of birch pollen allergen Bet v 1 induce blocking IgG in mice. Ganglberger E; Grunberger K; Wiedermann U; Vermes M; Sponer B; Breiteneder H; Scheiner O; Boltz G; Jensen-Jarolim E. (Department of Pathophysiology (formally Department of General and Experimental Pathology), University of Vienna, Austria.) INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (2001 Jan-Mar) 124 (1-3) 395-7. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB BACKGROUND: The induction of nonanaphylactogenic 'blocking' IgG antibodies capable of inhibiting the IgE/allergen interaction represents a favorable therapeutic concept for type I allergy. However, IgG antibodies to allergens may block or enhance specific IgE binding, depending on the recognized epitope. Taking the major birch pollen allergen Bet v 1 as a model, we developed a strategy for the precise induction of IgG antibodies of a desired epitope specificity. METHODS: Random phage display peptide libraries were applied to define peptide structures mimicking natural epitopes (mimotopes) of Bet v 1. Selections were performed with BIP 1, a murine monoclonal antibody known to enhance the IgE binding to Bet v 1, and with anti-Bet v 1 IgE purified from patients' sera. The characterized Bet v 1 mimotopes were used to localize the corresponding epitope at the surface of Bet v 1 by a computer-aided mathematical approach based on the three-dimensional structure and the chemical character of the amino acids. The Bet v 1 mimotopes were further used to immunize BALB/c mice. The specificity of the induced antibodies was tested by immunoblotting and inhibition assays. RESULTS: With the three-dimensional epitope search it became possible to localize a discontinuous IgE epitope on the surface of Bet v 1 in a substantial distance from the IgG epitope of the monoclonal antibody BIP 1. Moreover, we could demonstrate that phage displaying mimotopes are immunogenic vectors for the precise induction of epitope-specific IgG. Immunization with BIP 1 mimotopes induced IgG enhancing the IgE binding to Bet v 1, whereas immunization with **IgE mimotopes** resulted in IgG capable of blocking human IgE binding in vitro. CONCLUSION: Allergen mimotopes can be used for the induction of anti allergen IgG of desired specificity. We propose that mimotope immunotherapy based on **IgE mimotopes** generated by biopannings may represent a future concept for therapy of type I allergy.

L16 ANSWER 3 OF 9 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
2001:805862 The Genuine Article (R) Number: 478XE. Monovalent fusion proteins of immunoglobulin E mimotopes are safe for therapy of type I allergy. Ganglberger E; Sponer B; Scholl I; Wiedermann U; Baumann S; Hafner C; Breiteneder H; Suter M; Boltz-Nitulescu G; Scheiner O; Jensen-Jarolim E (Reprint). Univ Vienna, Sch Med, Dept Pathophysiol, AKH-3Q, Wahringer Gurtel 18-20, A-1090 Vienna, Austria (Reprint); Univ Vienna, Sch Med, Dept Pathophysiol, A-1090 Vienna, Austria; Univ Zurich, Dept Virol, CH-8057 Zurich, Switzerland. FASEB JOURNAL (SEP 2001) Vol. 15, No. 11, pp. U4-U19. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA. ISSN: 0892-6638. Pub. country: Austria; Switzerland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB By screening phage display random peptide libraries with purified immunoglobulin E (IgE) from birch pollen-allergic patients, we previously defined peptides mimicking natural IgE epitopes (mimotopes) of the major birch pollen allergen Bet v 1. The present study aimed to define a monovalent carrier for the **IgE mimotopes** to induce protective antibodies directed to the IgE epitopes, suitable for

mimotope-specific therapy. We expressed the selected mimotopes as fusion proteins together with streptococcal albumin binding protein (ABP). The fusion proteins were recognized specifically by anti-Bet v 1 human IgE, which demonstrated that the mimotopes fused to ABP resemble the natural IgE epitope. Bet v 1-specific IgG was induced by immunization of BALB/c mice with fusion proteins. These IgG antibodies could inhibit IgE binding to Bet v 1. Skin testing of Bet v 1 allergic mice showed that the ABP mimotope constructs did not elicit type I skin reactions, although they possess IgE binding structures. Our data suggest that **IgE mimotopes** are safe for epitope-specific immunotherapy of sensitized individuals, when presented in a monovalent form. Therefore, ABP-fused mimotopes are promising candidates for a new type of immunotherapy based on the precise induction of blocking antibodies.

L16 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
2000:608610 Document No. 133:206755 Immunogens comprising a peptide and a carrier derived from Haemophilus influenzae protein D. Coste, Michel; Lobet, Yves; Van-Mechelen, Marcelle Paulette; Verriest, Christophe (Smithkline Beecham Biologicals S.A., Belg.). PCT Int. Appl. WO 2000050077 A1 20000831, 53 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP1457 20000222. PRIORITY: GB 1999-4405 19990225; GB 1999-4408 19990225; GB 1999-4412 19990225; GB 1999-19260 19990813.

AB The present invention provides peptide immunogens linked to a carrier wherein the carrier is derived from Haemophilus Influenzae Protein D or fragments thereof. Compns comprising the antigen peptide, protein D epitope or mimotope, and immune adjuvant (e.g. saponin, aluminum salt, oil in water emulsion, or liposome) are useful for treating infection or chronic diseases.

L16 ANSWER 5 OF 9 MEDLINE on STN DUPLICATE 3
2001042128 Document Number: 20507634. PubMed ID: 11053238. Allergen mimotopes for 3-dimensional epitope search and induction of antibodies inhibiting human IgE. Ganglberger E; Grunberger K; Sponer B; Radauer C; Breiteneder H; Boltz-Nitulescu G; Scheiner O; Jensen-Jarolim E. (Department of Pathophysiology, AKH, Medical School, University of Vienna, A-1090 Vienna, Austria.) FASEB JOURNAL, (2000 Nov) 14 (14) 2177-84. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB There is no definite information available on the structural characteristics of IgE binding epitopes on allergenic molecules, although it is widely accepted that most of them are conformational. In the current study we aimed to characterize the IgE epitope of Bet v 1, the major birch pollen allergen, by the application of phage display peptide libraries. We purified IgE specific for Bet v 1 from allergic patients' sera to select mimotopes representing artificial IgE epitopes by biopanning of phage libraries. By linear alignment, it was not possible to attribute mimotope sequences to the primary structure of Bet v 1. We developed a computer-aided, 3-dimensional coarse-grained epitope search. The 3-dimensional search, followed by statistical analysis, revealed an exposed area on the Bet v 1 molecule (located between residues 9-22 and 104-123) as the IgE binding structure. The IgE epitope was located at a 30 A distance from a previously described IgG epitope and the respective mimotope, designated Bet mim E. Such mimotopes could potentially be used for the induction of IgG capable of interfering with the IgE/allergen interaction. To test this hypothesis, we immunized BALB/c mice with the phage-displayed Bet mim E. Immunizations resulted in the induction of Bet v 1-specific IgG, which was able to block the IgE binding to Bet v 1 in vitro. Based on these observations, we propose that immunotherapy with

IgE mimotopes generated by biopannings result in formation of blocking IgG. We conclude that mimotope immunotherapy may represent a new and promising concept for treatment of type I allergic disease.

L16 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
2000:53752 Document No. 132:346309 Regulation of immunoglobulin E inflammation: Anti-immunoglobulin E autoantibodies. Stadler, Beda M.; Vogel, Monique; Miescher, Sylvia Margaret; Zuercher, Adrian Walter; Rudolf, Michael P.; Kricek, Franz (University of Bern, Bern, Switz.). Lung Biology in Health and Disease, 136(Immunotherapy in Asthma), 431-438 (English) 1999. CODEN: LBHDD7. ISSN: 0362-3181. Publisher: Marcel Dekker, Inc..
AB A review with 43 refs. Discussed are: anti-IgE autoantibodies (occurrence; in vitro models for anti-IgE activity; isolation of anti-IgE autoantibodies by repertoire cloning); mimicry of IgE epitopes (epitope specificity and biol. activity of anti-IgE antibodies; **IgE mimotopes**); anti-idiotypic antibodies as epitope mimicry; and therapeutic strategies based on anti-IgE antibodies (passive immunization with humanized antibodies; active immunization).

L16 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
1998:612276 Document No. 129:289101 A mimotope defined by phage display inhibits IgE binding to the plant panallergen profilin. Leitner, Agnes; Vogel, Monique; Radauer, Christian; Breiteneder, Heimo; Stadler, Beda M.; Scheiner, Otto; Kraft, Dietrich; Jensen-Jarolim, Erika (Department General Experimental Pathology, University Vienna, Vienna, A-1090, Austria). European Journal of Immunology, 28(9), 2921-2927 (English) 1998. CODEN: EJIMAF. ISSN: 0014-2980. Publisher: Wiley-VCH Verlag GmbH.
AB Birch pollen and mugwort pollen allergies are often assocd. with hypersensitivity to plant foods. This clin. and serol. cross-reactivity is mediated by IgE antibodies reacting with homologous proteins in pollen and food. Cross-reacting homologs of the important birch pollen allergen Bet v 2 (profilin) were detected in other pollen, fruits, nuts, and vegetables, such as celery tuber. The authors purified IgG/IgE antibodies from the serum of an exclusively profilin-allergic patient using affinity columns either coupled with protein exts. from mugwort pollen, birch pollen, or celery tuber. Constrained and unconstrained random nonapeptide libraries were pooled and screened with the anti-profilin antibody prepns. to define cross-reactive ligands. Specific ligands were enriched by successive panning rounds using the profilin-specific antibodies in series. After the last panning round enriched phage clones were screened with purified profilin-specific antibodies and IgE-binding clones were sequenced. Five of 8 pos. clones (62.5%) displayed the same circular peptide CAISGGYPVC. This peptide was synthesized and examd. for its ability to inhibit IgE binding to blotted mugwort pollen, birch pollen, or celery tuber profilin. Inhibition studies showed redn. of IgE binding to profilins in all 3 protein exts. As the sequence of the mimotope did not show any homol. to the known birch profilin sequence this peptide is considered to mimic a common conformational IgE epitope for these examd. profilins.

L16 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
1998:145086 Document No. 128:242665 Anti-IgE vaccination. Stadler, Beda M.; Vogel, Monique; Rudolf, Michael; Miescher, Sylvia; Zurcher, Adrian; Kricek, Franz (Institute of Immunology and Allergology, University of Bern, Bern, Switz.). Progress in Allergy and Clinical Immunology, Proceedings of the International Congress of Allergology and Clinical Immunology, 16th, Cancun, Mex., Oct. 19-24, 1997, 339-342. Editor(s): Oehling, Albert K.; Huerta Lopez, J. G. Hogrefe & Huber: Seattle, Wash. (English) 1997. CODEN: 65SQAB.
AB A review with 34 refs. The phage display technol. has provided a new way to dissect the natural anti-IgE response. Based on the authors' results, the question can now be addressed whether it may be possible to redirect a human anti-IgE response by active immunization with **IgE**-

mimotopes or anti-idiotypic antibodies. To understand allergic disease, it can also be envisaged that a radical approach to eliminate or neutralize IgE will finally be the proof of how important the IgE mol. is for the pathophysiol. of the IgE mediated diseases.

L16 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 4
97276834 Document Number: 97276834. PubMed ID: 9130527. Can active immunization redirect an anti-IgE immune response?. Stadler B M; Rudolf M P; Vogel M; Miescher S; Zurcher A W; Kricek F. (Institute of Immunology and Allergology, Inselspital, Bern, Switzerland.. stadler@insel.unibe.ch) . INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, (1997 May-Jul) 113 (1-3) 216-8. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB We used as a template a mouse monoclonal antibody against IgE to isolate peptides from random peptide phage display libraries. Thereby, two types of peptides were isolated that corresponded to two different epitopes on the human IgE molecule. These peptides, also called mimotopes, seem to be a suitable tool in conjunction with carriers to induce an autoimmune response with a beneficial effect in humans, because the originally used template antibody is capable of neutralizing IgE, is nonanaphylactogenic, and inhibits IgE synthesis. The vaccination approach is further supported by the fact that we were capable of isolating anti-idiotypic antibodies from antibody phage display libraries against the template antibody. These anti-idiotypic antibodies were inhibited by both of the isolated **IgE mimotopes**. Thus, active vaccination with defined **IgE mimotopes** may represent a follow-up drug for the presently used anti-IgE antibodies.

```
=> s IgE peptide
L17          96 IGE PEPTIDE

=> s l17 and "EDGQVMDVD"
L18           0 L17 AND "EDGQVMDVD"

=> dup remove l17
PROCESSING COMPLETED FOR L17
L19          53 DUP REMOVE L17 (43 DUPLICATES REMOVED)

=> s l19 and C 2 domain
L20           0 L19 AND C 2 DOMAIN

=> s l19 and surface
L21           6 L19 AND SURFACE

=> dup remove l21
PROCESSING COMPLETED FOR L21
L22           6 DUP REMOVE L21 (0 DUPLICATES REMOVED)

=> d l22 1-6 cbib abs
```

L22 ANSWER 1 OF 6 MEDLINE on STN
2000263876 Document Number: 20263876. PubMed ID: 10801344. Mimicry of human IgE epitopes by anti-idiotypic antibodies. Vogel M; Miescher S; Kuhn S; Zurcher A W; Stadler M B; Ruf C; Effenberger F; Kricek F; Stadler B M. (Institute of Immunology and Allergology, Sahli Haus 2, Inselspital, 3010, Switzerland.) JOURNAL OF MOLECULAR BIOLOGY, (2000 May 19) 298 (5) 729-35. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB According to Jerne's network hypothesis, the binding site of an anti-idiotypic antibody also represents the internal image of an epitope present on a foreign, or even a self antigen. In recent years, antigen mimicry has been defined at the molecular level for some xeno-antigens. However, until now there has been no demonstration of structural mimicry between a human anti-idiotypic antibody and a self structure. To address

this question, we used human IgE as the self structure and a well-defined anti-human IgE mAb (BSW17). We describe the isolation of two anti-idiotypic antibodies specific for the anti-IgE antibody BSW17 from a non-immune human Fab phage display library. Interestingly, these two anti-idiotypic antibodies mimic the same molecular **surface** region as a previously described **IgE peptide** mimotope isolated by panning on BSW17, but they cover a much larger epitope on the IgE molecule. Accordingly, immunisation of rabbits with the two anti-idiotypic antibodies induced high-affinity antibodies with the same characteristics as BSW17. Thus, our data demonstrate that it is possible to isolate anti-idiotypic antibodies derived from the human genome without the need for hyperimmunization, and confirm Jerne's hypothesis that both foreign antigens and self structures can be mimicked by our own immunoglobulins.

L22 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN
1999:691112 Document No. 131:321535 Peptide antagonists of CD8. Korngold, Robert; Huang, Ziwei; Choksi, Swati (Thomas Jefferson University, USA). PCT Int. Appl. WO 9954345 A1 19991028, 68 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US8814 19990421. PRIORITY: US 1998-82436 19980421.
AB The authors disclose peptides that inhibit CD8-mediated T cell activation and that have a mol. **surface** that corresponds to human CD8.alpha. at amino acids 73-76 and/or 38-46 and/or 53-56 and/or 60-67. In one example, a conformationally-restricted cyclic peptide representing residues 71-78 of human CD8 was shown to inhibit the effector function of cytotoxic T-cells directed to chronic myelogenous leukemia. In a second example, the human peptide, and the murine homolog, was shown to prolong the survival of skin allografts in mouse. The application of these CD8 antagonists in treatment of graft vs. host disease and/or organ rejection are discussed.

L22 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN
1996:333073 Document No. 125:8486 Peptides representing antigenic epitopes of dog IgE present on B cell but not basophil **surface**. Chang, Tse W. (Tanox Biosystems, Inc., USA). U.S. US 5514776 A 19960507, 6 pp., Cont.-in-part of U.S. Ser. No. 137, 253. (English). CODEN: USXXAM. APPLICATION: US 1994-326767 19941020. PRIORITY: US 1987-140036 19871231; US 1988-226421 19880729; US 1988-229178 19880805; US 1988-272243 19881116; US 1989-369625 19890621; US 1990-468766 19900123; US 1990-515604 19900427; US 1992-973321 19921029; US 1993-90527 19930709; US 1993-137253 19931014.
AB Antigenic epitopes assocd. with the extracellular segment of the domain which anchors dog Ig-.epsilon. (or .epsilon..mb/ec) to the B cell membrane are disclosed. The epitopes are present on dog IgE-bearing B cells but not basophils or the secreted, sol. form of dog IgE. The peptides representing the epitopes assocd. with the anchor domain of dog IgE can be used to generate antibodies against these regions. Sequencing of the dog .epsilon..mb/ec segment was described, but no sequence was presented. Development of antibodies to the dog .epsilon..mb/ec segment for diagnostic uses was also stated.

L22 ANSWER 4 OF 6 MEDLINE on STN
97072938 Document Number: 97072938. PubMed ID: 8915686. Inhibition of antigen-specific IgE production by antigen coupled to membrane **IgE peptide**. Chen S S; Schmaltz R; Wang Y Y; Kong Q X; Petro T; Li Q; Chang T W. (Department of Veterinary and Biomedical Science, IANR, University of Nebraska-Lincoln, USA.) IMMUNOLOGICAL INVESTIGATIONS, (1996 Sep-Nov) 25 (5-6) 495-505. Journal code: 8504629. ISSN: 0882-0139. Pub. country: United States. Language: English.
AB The membrane **IgE peptide** (MEP) encompassing 20 amino acids proximal to the C terminus of membrane IgE molecules, and secretory **IgE p ptides** (SEP), spanning CH epsilon 1 to 4 domain were synthesized according to IgE genomic and cDNA sequences. Inhibition

of anti-KLH and anti-BGG IgE, but not IgG responses was observed in mice treated with MEP-protein but not SEP-protein conjugates in complete/incomplete Freund's adjuvant. Only IgE responses directed toward proteins to which MEP was conjugated, were inhibited, while IgE responses to a concomitantly injected, unrelated antigen were not. Inhibition of antigen-specific IgE was also not correlated with levels of anti-MEP or anti-IgE antibodies, moreover, levels of total IgE remained comparable among mice treated with MEP-protein conjugates, native or glutaraldehyde-modified protein carriers. This observation may have significant import on future design of IgE immunotherapy. Treatment of MEP conjugated allergens prevents formation of IgE-anti-IgE complexes because the MEP sequence is absent from the secretory IgE.

L22 ANSWER 5 OF 6 MEDLINE on STN
87190681 Document Number: 87190681. PubMed ID: 2952512. Inhibition of binding of rat IgE to rat mast cells by synthetic **IgE peptides**. Burt D S; Stanworth D R. EUROPEAN JOURNAL OF IMMUNOLOGY, (1987 Mar) 17 (3) 437-40. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY, WEST: Germany, Federal Republic of. Language: English.
AB Seven synthetic peptides corresponding to amino acid sequences located within various **surface** regions of the CH3 and CH4 domains of rat IgE were tested for their capacity to compete with intact rat IgE for binding sites on mast cells. Peptides representing rat IgE sequences 414-428 (P129), 459-472 (P124), 491-503 (P128) and 542-557 (P123) inhibited the binding of 125I-labeled rat IgE to mast cells by between 25-50% at concentrations between 10(-5)-10(-4) M. Three other rat IgE sequences, 378-396 (P130), 522-535 (P122) and 560-571 (P131), and three non-**IgE peptides** demonstrated no inhibitory activity.
On a molar basis, the most active peptide, P129, was approximately 1000-times less active than native rat IgE. Furthermore, extensive washing of cells incubated with this peptide did not reduce its ability to inhibit the subsequent binding of 125I-labeled rat IgE. These results suggest that residues within sequences 414-428, 459-473, 491-503 and 542-557 may contribute towards the mast cell receptor binding site on rat IgE.

L22 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN
1988:526981 Document No. 109:126981 Use of synthetic peptides in the delineation of the role of non-antigen receptors in mast cell signalling processes. Stanworth, D. R. (Rheumatol. Allergy Res. Unit, Univ. Birmingham, Birmingham, B15 2TJ, UK). Advances in Experimental Medicine and Biology, 225(Immunobiol. Proteins Pept. 4: T-Cell Recognit. Antigen Prese), 213-22 (English) 1987. CODEN: AEMBAP. ISSN: 0065-2598.
AB Previous expts. identified rat Ig .epsilon.-chain-derived peptides which apparently contribute to the Fc(.epsilon.) receptor binding activity of the Ig mol. Here it was shown that antibodies against sequences 378-396 in the C.epsilon.3 domain and against 3 sequences (459-472, 522-535, and 542-557) in the C.epsilon.4 domain are reactive with receptor-occupied IgE mols. Computer graphics modeling indicated that at least some of the peptides implicated in the binding of IgE to mast cells form a continuous part of the IgE mol. **surface**, which could constitute a lateral Fc(.epsilon.) receptor binding site.

=> s IgE vaccine
L23 12 IGE VACCINE

=> dup remove l23
PROCESSING COMPLETED FOR L23
L24 8 DUP REMOVE L23 (4 DUPLICATES REMOVED)

=> d l24 1-8 cbib abs

L24 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
2002:571256 Document No. 137:168144 Long-term protective and

antigen-specific effect of heat-killed Mycobacterium vaccae in a murine model of allergic pulmonary inflammation. Zuany-Amorim, Claudia; Manlius, Corinne; Trifilieff, Alexandre; Brunet, Laura R.; Rook, Graham; Bowen, Gareth; Pay, Graham; Walker, Christoph (Novartis Horsham Research Center, Novartis Pharmaceutical Ltd., Horsham, UK). Journal of Immunology, 169(3), 1492-1499 (English) 2002. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB This report examines the effect of heat-killed Mycobacterium vaccae in a mouse model of allergic pulmonary inflammation. The s.c. administration of M. vaccae 3 wk before the immunization significantly reduced Ag-induced airway hyperreactivity and the increase in the nos. of eosinophils obsd. in the bronchoalveolar lavage fluid, blood, and bone marrow, even though no detectable changes in either cytokine (IL-4, IL-13, IL-5, and IFN-.gamma.) or total IgE levels were obsd. Furthermore, transfer of splenocytes from OVA-immunized and M. vaccae-treated mice into recipient, OVA-immunized mice significantly reduced the allergen-induced eosinophilia by an IFN-.gamma.-independent mechanism, clearly indicating that the mechanism by which M. vaccae induces its inhibitory effect is not due to a redirection from a predominantly Th2 to a Th1-dominated immune response. The protective effect of M. vaccae on the allergen-induced eosinophilia lasted for at least 12 wk after its administration, and the treatment was also effective in presensitized mice. Moreover, the allergen specificity of the inhibitory effect could be demonstrated using a double-immunization protocol, where M. vaccae treatment before OVA immunization had no effect on the eosinophilic inflammation induced by later immunization and challenge with cockroach ext. Ag. Taken together, these results clearly demonstrate that M. vaccae is effective in blocking allergic inflammation by a mechanism independent of IFN-.gamma., induces long term and Ag-specific protection, and therefore has both prophylactic and therapeutic potential for the treatment of allergic diseases.

L24 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN

2002:439831 Document No. 137:61769 Generation of therapeutic antibody responses against IgE through vaccination. Vernersson, Molly; Ledin, Anna; Johansson, Jeannette; Hellman, Lars (Department of Cell and Molecular Biology, Biomedical Center, University of Uppsala, Uppsala, S-751 24, Swed.). FASEB Journal, 16(8), 875-877, 10.1096/fj.01-0879fje (English) 2002. CODEN: FAJOEC. ISSN: 0892-6638. Publisher: Federation of American Societies for Experimental Biology.

AB IgE is the central mediator in atopic allergies such as hay fever, eczema, and asthma; therefore, it is a prime target in the development of allergen-independent preventive treatments. We describe an active immunization strategy that has the potential to reduce IgE to a clin. significant extent. The active vaccine component is a chimeric IgE mol., C.vepsiln.2-C.vepsiln.3-C.vepsiln.4. The receptor-binding target domain, C.vepsiln.3, is derived from the recipient species, whereas the flanking domains, C.vepsiln.2 and C.vepsiln.4, are derived from an evolutionarily distant mammal. The flanking domains have dual functions, acting both as structural support for the C.vepsiln.3 domain and to break T cell tolerance by providing foreign T cell epitopes. The efficacy of the vaccine was studied in an ovalbumin-sensitized rat model. Vaccination resulted in antibody responses against IgE in all rats and in a substantial redn. in serum IgE levels in three out of four strains. The skin reactivity upon allergen challenge was significantly reduced in vaccinated animals. The vaccine appears to be safe to use as an antigen. No crosslinking activity was obsd. in sera of vaccinated animals, and the response to vaccination was reversible with time. Our results suggest that active immunization against IgE has the potential to become a therapeutic method for humans.

L24 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN

2002:277919 Document No. 137:167729 Recombinant allergens for immunotherapy. Chapman, Martin D.; Smith, Alisa M.; Vailes, Lisa D.; Pomes, Anna (Asthma and Allergic Diseases Center, University of Virginia, Charlottesville, VA, 22903, USA). Allergy and Asthma Proceedings, 23(1), 5-8 (English) 2002.

CODEN: AAPRFV. ISSN: 1088-5412. Publisher: OceanSide Publications, Inc..

AB A review. Many of the problems assocd. with using natural allergenic products for allergy diagnosis and treatment can be overcome using genetically engineered recombinant allergens. Over the past 10 yr, the most important allergens from mites, pollens, animal dander, insects, and foods have been cloned, sequenced, and expressed. Allergens have diverse biol. functions (they may be enzymes, enzyme inhibitors, lipocalins, or structural proteins). High-level expression systems have been developed to produce recombinant allergens in bacteria, yeast, or insect cells. Recombinant allergens show comparable IgE antibody binding to natural allergens and show excellent reactivity on skin testing and in in vitro diagnostic tests. Recombinant allergens will enable innovative new strategies for allergen immunotherapy to be developed. These include peptide-based vaccines, engineered hypo-allergens with reduced reactivity for IgE antibodies, nucleotide-conjugated vaccines that promote Th1 responses, and the possibility of developing prophylactic allergen vaccines.

L24 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN

2001:635924 Document No. 135:194487 Methods of prevention and treatment of asthma and allergic conditions. Sukurkovich, Boris; Skurkovich, Simon (Advanced Biotherapy, Inc., USA). PCT Int. Appl. WO 2001062287 A1 20010830, 84 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US5660 20010223. PRIORITY: US 2000-511972 20000224.

AB The present invention relates to allergy vaccines and methods of treating and/or preventing asthma, and allergic conditions. The invention is based on the discovery that inhibiting the ligand/receptor interactions involving, e.g., IgE, IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, interferon-alpha, histamine, leukotriene, and their resp. receptors, inhibits prodn. of IgE thereby treating or preventing such diseases or conditions. Competitive inhibition of such receptor/ligand interactions is accomplished by immunizing a human or veterinary patient with the interleukin, interferon-alpha, histamine, leukotriene, their receptors, in any combination. Also, the invention relates to inhibiting receptor/ligand interactions involved in IgE prodn. by competitively inhibiting such interactions by administering antibodies to the ligands, receptors, or both, as well as by administering analogs of the receptors (e.g., sol. receptors not assocd. with a cell).

L24 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN

2000:314492 Document No. 132:346610 Enhanced vaccines. Hellman, Lars T. (Resistentia Pharmaceuticals AB, Swed.). PCT Int. Appl. WO 2000025722 A2 20000511, 50 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-SE1896 19991021. PRIORITY: US 1998-PV106652 19981102; US 1999-401636 19990922.

AB The invention relates to methods and materials involved in the treatment and prevention of various diseases such as infections and IgE-related diseases. Specifically, the invention relates to methods and materials that can be used to vaccinate a mammal against specific self or non-self antigens. For example, the methods and materials described herein can be used to reduce the effects of IgE antibodies within a mammal by reducing the amt. of total and receptor bound IgE antibodies in the mammal. In addn., the invention provides vaccine conjugates, immunogenic polypeptides, nucleic acid mols. that encode immunogenic polypeptides, host cells contg. the nucleic acid mols. that encode immunogenic polypeptides, and methods for making vaccine conjugates and immunogenic polypeptides as well as nucleic acid mols. that encode immunogenic

polypeptides. Further, the invention provides an **IgE vaccin** that induces an anti-self IgE response in a mammal.

L24 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 1
2000069385 Document Number: 20069385. PubMed ID: 10602034. Oral anti-IgE immunization with epitope-displaying phage. Zuercher A W; Miescher S M; Vogel M; Rudolf M P; Stadler M B; Stadler B M. (Institute of Immunology, University of Bern, Inselspital, Bern, Switzerland.) EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Jan) 30 (1) 128-35. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB An essential requirement for oral vaccines is the ability to survive the harsh environment of the stomach in an antigenically intact form. As bacteriophages are adapted to this environment we used epitope-displaying M13 bacteriophages as carriers for an experimental oral anti-**IgE vaccine**. The feasibility of this approach was tested in a simulated gastric fluid using two different mimotopes as well as an anti-idiotypic Fab of the non-anaphylactogenic monoclonal anti-IgE antibody BSW17. All phage clones remained infective after this treatment. However, only epitopes displayed on the pVIII protein were still recognized by BSW17 whereas pIII-expressed epitopes were rapidly inactivated. Surprisingly, when used for oral immunization of mice all phage clones induced anti-IgE antibodies. In contrast, oral immunization with the purified, pVIII protein displaying the mimotope induced anti-phage but no anti-IgE antibodies. After feeding a single dose of mimotope-displaying bacteriophage, phage DNA could be detected in mouse feces for 10 days. Our results show that epitope-displaying bacteriophages can be used to induce an epitope-specific antibody response via the oral route.

L24 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
2000:244696 Document No. 133:57193 Immunotherapy for food allergies: past, present, future. Lehrer, Samuel B.; Wild, Laurianne G.; Bost, Kenneth L.; Sorensen, Ricardo U. (Division of Allergy and Clinical Immunology, Department of Medicine, Tulane University Medical Center, New Orleans, LA, USA). Clinical Reviews in Allergy & Immunology, 17(3), 361-381 (English) 1999. CODEN: CRAIF2. ISSN: 1080-0549. Publisher: Humana Press Inc..

AB A review with 65 refs. An overview of the gut mucosal immune response, along with the traditional and novel approaches to immunotherapy such as immune complex therapy, peptide therapy, anti-IgE and DNA immunization are discussed. A discussion of mucosal vaccines and advances in the development of hypo-allergenic foods through biotechnol. to reduce IgE binding capacity of the allergenic proteins is also presented.

L24 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
1998:145086 Document No. 128:242665 Anti-IgE vaccination. Stadler, Beda M.; Vogel, Monique; Rudolf, Michael; Miescher, Sylvia; Zurcher, Adrian; Kricek, Franz (Institute of Immunology and Allergology, University of Bern, Bern, Switz.). Progress in Allergy and Clinical Immunology, Proceedings of the International Congress of Allergology and Clinical Immunology, 16th, Cancun, Mex., Oct. 19-24, 1997, 339-342. Editor(s): Oehling, Albert K.; Huerta Lopez, J. G. Hogrefe & Huber: Seattle, Wash. (English) 1997. CODEN: 65SQAB.

AB A review with 34 refs. The phage display technol. has provided a new way to dissect the natural anti-IgE response. Based on the authors' results, the question can now be addressed whether it may be possible to redirect a human anti-IgE response by active immunization with IgE-mimotopes or anti-idiotypic antibodies. To understand allergic disease, it can also be envisaged that a radical approach to eliminate or neutralize IgE will finally be the proof of how important the IgE mol. is for the pathophysiol. of the IgE mediated diseases.

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L25 8740 (FRIEDE M?/AU OR GREENWOOD J?/AU OR HEWITT E?/AU OR LAMONT A?/AU OR RANDALL R?/AU OR MASON S?/AU OR TURNELL W?/AU OR VAN MECHELE N M?/AU OR DE BASSOLS C?/AU)

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L27 15 DUP REMOVE L26 (11 DUPLICATES REMOVED)

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L27 ANSWER 1 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
2003:336219 Drugs affecting **IgE** (synthesis inhibitors and monoclonal antibodies). Garland, Lawrence G.; **Lamont, Alan G.** (Acambis PLC, Cambridge, UK). Drugs for the Treatment of Respiratory Diseases, 195-217. Editor(s): Spina, Domenico. Cambridge University Press: Cambridge, UK. ISBN: 0-521-77321-0 (English) 2003. CODEN: 69DVGJ.
AB A review describes the progress that has been made using various strategies to decrease both **IgE** prodn. and activity. It also briefly describes the regulation of **IgE** synthesis and the role of cytokines in the increase or decrease of the synthesis.

L27 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
2002:157814 Document No. 136:215424 Cyclized peptides of **IgE** for allergy immunotherapy. **Friede, Martin**; **Mason, Sean**; **Turnell, William Gordon**; Vinals y Bassols, Carlota (Smithkline Beecham Biologicals S.A., Belg.; Peptide Therapeutics Limited). PCT Int. Appl. WO 2002016409 A2 20020228, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP9576 20010817. PRIORITY: GB 2000-20717 20000822.
AB The authors disclose a process for the covalent conjugation of disulfide bridge cyclized peptides to immunogenic carrier mols. by thioether linkages to form vaccine immunogens. In particular, the process involves reacting a thiolated carrier with a maleimide-derivatized cyclic peptide. In one example, the authors prep. immunogens based on peptides derived from the sequence of human **IgE**. Immunization with the cyclic peptide-carrier protein produced IgG antibodies with the ability to block histamine release by human basophils.

L27 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
2000:608781 Document No. 133:206772 Epitopes or mimotopes derived from the C-epsilon-3 or C-epsilon-4 domains of **IgE**, antagonists thereof, and their therapeutic uses. **Friede, Martin**; **Mason, Sean** ; **Turnell, William Gordon**; **Van Mechelen, Marcelle Paulette**; **De Bassols, Carlota Vinals Y.** (Smithkline Beecham Biologicals S.A., Belg.; Peptide Therapeutics Ltd.). PCT Int. Appl. WO 2000050461 A1 20000831, 76 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP1456 20000222. PRIORITY: GB 1999-4408 19990225; GB 1999-17144 19990721; GB 1999-18598 19990807; GB 1999-18599 19990807; GB 1999-18601

19990807; GB 1999-18604 19990807; GB 1999-18606 19990807; GB 1999-25618 19991029.

AB The present invention relates to the provision of novel medicaments for the treatment, prevention or amelioration of allergic disease. In particular, the novel medicaments are epitopes or mimotopes derived from the C.epsilon.3 or C.epsilon.4 domains of **IgE**. These novel regions may be the target for both passive and active immunoprophylaxis or immunotherapy. The invention further relates to methods for prodn. of the medicaments, pharmaceutical compns. contg. them and their use in medicine. Also forming an aspect of the present invention are ligands, esp. monoclonal antibodies, which are capable of binding the **IgE** regions of the present invention, and their use in medicine as passive immunotherapy or immunoprophylaxis.

L27 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

2000:608780 Document No. 133:206771 Epitopes or mimotopes derived from the C.epsilon.2 domain of **IgE**, antagonists thereof, and their therapeutic uses. Dyson, Michael; **Friede, Martin**; **Greenwood, Judith**; **Hewitt, Ellen**; **Lamont, Alan** ; **Mason, Sean**; **Randall, Roger**; **Turnell, William Gordon**; **Van Mechelen, Marcelle Paulette**; Vinals y De Bassols, Carlota (Smithkline Beecham Biologicals S.A., Belg.; Peptide Therapeutics Limited). PCT Int. Appl. WO 2000050460 A1 20000831, 129 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP1455 20000222. PRIORITY: GB 1999-4405 19990225; GB 1999-7151 19990329; GB 1999-10537 19990507; GB 1999-10538 19990507; GB 1999-18594 19990807; GB 1999-18603 19990807; GB 1999-21046 19990907; GB 1999-21047 19990907; GB 1999-25619 19991029; GB 1999-27698 19991123.

AB The present invention relates to the provision of novel medicaments for the treatment, prevention or amelioration of allergic disease. In particular, the novel medicaments are isolated peptides incorporating epitopes or mimotopes of surface exposed regions of the C<e2 domain of **IgE**. The inventors have found that these novel regions may be the target for both passive and active immunoprophylaxis or immunotherapy. The invention further relates to methods for prodn. of the medicaments, pharmaceutical compns. contg. them and their use in medicine. Also forming an aspect of the present invention are ligands, esp. monoclonal antibodies, which are capable of binding the surface exposed **IgE** regions of the present invention, and their use in medicine as passive immunotherapy or in immunoprophylaxis.

L27 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

2000:608610 Document No. 133:206755 Immunogens comprising a peptide and a carrier derived from Haemophilus influenzae protein D. Coste, Michel; Lobet, Yves; **Van-Mechelen, Marcelle Paulette**; Verriest, Christophe (Smithkline Beecham Biologicals S.A., Belg.). PCT Int. Appl. WO 2000050077 A1 20000831, 53 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP1457 20000222. PRIORITY: GB 1999-4405 19990225; GB 1999-4408 19990225; GB 1999-4412 19990225; GB 1999-19260 19990813.

AB The present invention provides peptide immunogens linked to a carrier wherein the carrier is derived from Haemophilus Influenzae Protein D or

fragments thereof. Compns comprising the antigen peptide, protein D epitope or mimotope, and immune adjuvant (e.g. saponin, aluminum salt, oil in water emulsion, or liposome) are useful for treating infection or chronic diseases.

L27 ANSWER 6 OF 15 MEDLINE on STN DUPLICATE 1

2000392733 Document Number: 20308139. PubMed ID: 10848897. Functional effects of the inhibition of the cysteine protease activity of the major house dust mite allergen Der p 1 by a novel peptide-based inhibitor. John R J; Rusznak C; Ramjee M; **Lamont A G**; Abrahamson M; **Hewitt E L**. (*Peptide Therapeutics Ltd, Biology Department, Peterhouse Technology Park, Cambridge, UK.*) CLINICAL AND EXPERIMENTAL ALLERGY, (2000 Jun) 30 (6) 784-93. Journal code: 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: The house dust mite (HDM) Dermatophagoides pteronyssinus is an important source of allergens, which can cause allergic conditions. The cysteine protease activity of Der p 1 may enhance the potency of this major mite allergen through cleavage of CD23 and CD25 from the surface of immune cells, **IgE** independent mast cell activation, increases in epithelial cell permeability and inactivation of an endogenous serine protease inhibitor. Inhibition of the enzymatic activity of Der p 1 may therefore be of therapeutic benefit. OBJECTIVE: To examine the activity of PTL11028, a newly developed Der p 1 inhibitor, in a range of assays that directly or indirectly measure Der p 1 protease activity and to compare its activity to endogenous cysteine protease inhibitors. METHODS: The proteolytic activities of purified Der p 1 or HDM extract and inhibitory properties of PTL11028 were examined through cleavage of an artificial peptidyl substrate, cleavage of CD23 from human B cells and permeability studies on primary human bronchial epithelial cells. RESULTS: PTL11028 is a highly potent and specific Der p 1 inhibitor, being effective against both purified protease and Der p 1 within HDM extract. PTL11028 can completely inhibit Der p 1-mediated CD23 cleavage from human B cells and also reduces HDM-induced human bronchial epithelial cell permeability by 50%. Der p 1 is potently inhibited by cystatin A and to a lesser extent by cystatins C and E/M. CONCLUSION: PTL11028 is a highly potent and selective irreversible inhibitor of the cysteine protease activity of Der p 1, an activity that may be modulated in vivo by some human cystatins. PTL11028 prevents the Der p 1-mediated cleavage of CD23 from human B cells and significantly reduces HDM-induced permeabilization of the epithelial barrier. PTL11028 is an important tool to examine the biological effects of Der p 1 in a range of in vitro and in vivo model systems.

L27 ANSWER 7 OF 15 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN

1999:561201 The Genuine Article (R) Number: 216HW. Characterization and immunolocalization of a cytosolic calcium-binding protein from Brassica napus and Arabidopsis pollen. Rozwadowski K (Reprint); Zhao R H; Jackman L; Huebert T; Burkhart W E; Hemmingsen S M; **Greenwood J**; Rothstein S J. AGR & AGRI FOOD CANADA, 107 SCI PL, SASKATOON, SK S7N 0X2, CANADA (Reprint); UNIV GUELPH, DEPT MOL BIOL & GENET, GUELPH, ON N1G 2W1, CANADA; UNIV GUELPH, DEPT BOT, GUELPH, ON N1G 2W1, CANADA; NATL RES COUNCIL CANADA, INST PLANT BIOTECHNOL, SASKATOON, SK S7N 0W9, CANADA; GLAXO RES LABS, RES TRIANGLE PK, NC 27709. PLANT PHYSIOLOGY (JUL 1999) Vol. 120, No. 3, pp. 787-797. Publisher: AMER SOC PLANT PHYSIOLOGISTS. 15501 MONONA DRIVE, ROCKVILLE, MD 20855. ISSN: 0032-0889. Pub. country: CANADA; USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Two low-molecular-weight proteins have been purified from Brassica napus pollen and a gene corresponding to one of them has been isolated. The gene encodes an 8.6-kD protein with two EF-hand calcium-binding motifs and is a member of a small gene family in B. napus. The protein is part of a family of pollen allergens recently identified in several evolutionarily distant dicot and monocot plants. Homologs have been detected in Arabidopsis, from which one gene has been cloned in this study, and in snapdragon (Antirrhinum majus), but not in tobacco (Nicotiana tabacum).

Expression of the gene in B. napus was limited to male tissues and occurred during the pollen-maturation phase of anther development. Both the B. napus and Arabidopsis proteins interact with calcium, and the potential for a calcium-dependent conformational change was demonstrated. Given this affinity for calcium, the cloned genes were termed BPC1 and APC1 (B. napus and Arabidopsis pollen calcium-binding protein 1, respectively). Immunolocalization studies demonstrated that BPC1 is found in the cytosol of mature pollen. However, upon pollen hydration and germination, there is some apparent leakage of the protein to the pollen wall. BPC1 is also concentrated on or near the surface of the elongating pollen tube. The essential nature of calcium in pollen physiology, combined with the properties of BPC1 and its high evolutionary conservation suggests that this protein plays an important role in pollination by functioning as a calcium-sensitive signal molecule.

L27 ANSWER 8 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2000:155440 Document No.: PREV200000155440. Characterisation of novel anti-human **IgE** antibodies: 3. Functional effects in human basophils, human lung mast cells and RBL cells. **Randall, Roger** [Reprint author]; Dineley, Liz [Reprint author]; **Lamont, Alan** [Reprint author]. Peptide Therapeutics, 100 Fulbourn Road, Cambridge, CB1 9PT, UK. Immunology, (Dec., 1999) Vol. 98, No. suppl. 1, pp. 143. print.
Meeting Info.: Joint Congress of the British Society for Immunology and the British Society for Allergy and Clinical Immunology. Harrogate, England, UK. November 30-December 03, 1999. British Society for Allergy and Clinical Immunology; British Society for Immunology.
CODEN: IMMUAM. ISSN: 0019-2805. Language: English.

L27 ANSWER 9 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2000:155439 Document No.: PREV200000155439. Characterisation of novel anti-human **IgE** monoclonal antibodies: 2. Effects on interaction of **IgE** with FcepsilonRII. Stober, C. [Reprint author]; **Lamont, A. G.** [Reprint author]; **Hewitt, E. L.** [Reprint author]. Peptide Therapeutics, 100 Fulbourn Road, Peterhouse Technology Park, Cambridge, UK. Immunology, (Dec., 1999) Vol. 98, No. suppl. 1, pp. 143. print.
Meeting Info.: Joint Congress of the British Society for Immunology and the British Society for Allergy and Clinical Immunology. Harrogate, England, UK. November 30-December 03, 1999. British Society for Allergy and Clinical Immunology; British Society for Immunology.
CODEN: IMMUAM. ISSN: 0019-2805. Language: English.

L27 ANSWER 10 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2000:155438 Document No.: PREV200000155438. Characterisation of novel anti-human **IgE** monoclonal antibodies: 1. Effects on interaction of **IgE** with FcepsilonRI. **Mason, Sean** [Reprint author]; Stober, Carmel [Reprint author]; Gewert, Conny [Reprint author]; **Lamont, Alan** [Reprint author]; **Hewitt, Ellen** [Reprint author]. Peptide Therapeutics Ltd., 100 Fulbourn Road, Peterhouse Technology Park, Cambridge, CB1 9PT, UK. Immunology, (Dec., 1999) Vol. 98, No. suppl. 1, pp. 143. print.
Meeting Info.: Joint Congress of the British Society for Immunology and the British Society for Allergy and Clinical Immunology. Harrogate, England, UK. November 30-December 03, 1999. British Society for Allergy and Clinical Immunology; British Society for Immunology.
CODEN: IMMUAM. ISSN: 0019-2805. Language: English.

L27 ANSWER 11 OF 15 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2000:155427 Document No.: PREV200000155427. A reliable method for **IgE** -mediated degranulation from passively sensitised non-allergic human basophils. Dineley, Liz [Reprint author]; **Randall, Roger** [Reprint author]; **Lamont, Alan** [Reprint author]. Peptide Therapeutics, 100 Fulbourn Road, Cambridge, CB1 9PT, UK. Immunology, (Dec., 1999) Vol. 98, No. suppl. 1, pp. 140. print.
Meeting Info.: Joint Congress of the British Society for Immunology and

the British Society for Allergy and Clinical Immunology. Harrogate, England, UK. November 30-December 03, 1999. British Society for Allergy and Clinical Immunology; British Society for Immunology. CODEN: IMMUAM. ISSN: 0019-2805. Language: English.

L27 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

1998:795041 Document No. 130:51333 Human MAFA peptides for treating inflammation and allergy. **Hewitt, Ellen Louise**; Lamers, Maria Bardina Antonia Cornelia; **Lamont, Alan**; Williams, David Hugh (Peptide Therapeutics Limited, UK). PCT Int. Appl. WO 9854209 A2 19981203, 44 pp. *DESIGNATED STATES*: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-GB1572 19980529. PRIORITY: GB 1997-11148 19970531.

AB This invention relates to polypeptides, nucleotide sequences, antibodies or fragments thereof, ligands and compns. and their use in the medical fields of inflammation and allergy, disease examples of which include rheumatoid arthritis and asthma. These human MAFA peptides prevent cell activation, i.e. interleukin 2 release from T cells and **IgE** -mediated degranulation of basophils, as well as prevention of tumor growth.

L27 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

1998:4340 Document No. 128:74242 Dendritic cells and macrophages induce the development of distinct T helper cell populations in vivo. De Becker, Genevieve; Moulin, Veronique; **Van Mechelen, Marcelle**; Tielemans, Francoise; Urbain, Jacques; Leo, Oberdan; Moser, Muriel (Lab. Physiol. ANimale, Univ. Libre Bruxelles, Rhode-Saint-Genes, B-1640, Belg.). Advances in Experimental Medicine and Biology, 417(Dendritic Cells in Fundamental and Clinical Immunology, Vol. 3), 369-373 (English) 1997. CODEN: AEMBAP. ISSN: 0065-2598. Publisher: Plenum Publishing Corp..

AB Previously, the authors have shown that the injection of antigen-pulsed dendritic cells (DC) induces the synthesis of specific IgG1 and IgG2a antibodies, whereas macrophages favor the prodn. of IgG1 and **IgE** antibodies specific for the antigen. These data indicate that the isotype and the amplitude of the B-cell response can be regulated by the nature of the antigen-presenting cell. In this report, the authors directly evaluate Th1 and Th2 functions in lymph nodes of mice that were immunized by injection of dendritic cells or peritoneal macrophages pulsed with the antigen. The authors show that macrophages induce Th2 differentiation in vivo, whereas DC drive the development of cells able to secrete Th1 and Th2 cytokines.

L27 ANSWER 14 OF 15 MEDLINE on STN DUPLICATE 2

92251164 *Document Number*: 92251164. PubMed ID: 1578132. Therapy with monoclonal antibodies. An in vivo model for the assessment of therapeutic potential. Isaacs J D; Clark M R; **Greenwood J**; Waldmann H. (Department of Pathology (Immunology Division), University of Cambridge, United Kingdom.) JOURNAL OF IMMUNOLOGY, (1992 May 15) 148 (10) 3062-71. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB A set of rat-human and rat-rat chimeric mAb has been created, all possessing V regions identical in their specificity for the mouse CD8 Ag. In vitro all antibodies were able to block cell-mediated lysis but varied greatly in their capacity to utilize rabbit complement. We examined the ability of these chimeric antibodies to deplete in vivo and established a clear hierarchy. Of the human IgG subclasses, only IgG1, 2, and 3 could fix complement in vitro, yet all (IgG1-4) were remarkably potent at depleting CD8+ PBL in vivo. In contrast, human IgA2 and **IgE** were ineffective at clearing CD8+ PBL. The vector system used to create

these antibodies together with the small doses of antibodies required to deplete in vivo make this a simple and rapid system for testing the effects of different antibody isotypes and mutants. We have shown that a mutant of human IgG1, which is incapable of fixing complement, depletes perfectly well in vivo, whereas an aglycosyl IgG1 mutant is rendered inactive. Our model provides a unique opportunity to study effector functions and motifs that are used by mAb in vivo and will help in the design of improved antibodies for human therapy.

L27 ANSWER 15 OF 15 MEDLINE on STN DUPLICATE 3

92113483 Document Number: 92113483. PubMed ID: 1370533. The injection of deaggregated gamma globulins in adult mice induces antigen-specific unresponsiveness of T helper type 1 but not type 2 lymphocytes. De Wit D; **Van Mechelen M**; Ryelandt M; Figueiredo A C; Abramowicz D; Goldman M; Bazin H; Urbain J; Leo O. (Department de Biologie Moleculaire, Universite Libre de Bruxelles, Belgium.) JOURNAL OF EXPERIMENTAL MEDICINE, (1992 Jan 1) 175 (1) 9-14. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Injection of adult mice with high doses of monomeric human gamma globulins (dHGG) has been previously shown to produce a state of peripheral tolerance in both B and T cells. To gain insight into the mechanism of induction and maintenance of adult tolerance in this model, we have analyzed the pattern of lymphokines produced by control and tolerant animals in response to the tolerogen. The data presented indicate that HGG-specific, interleukin 2 (IL-2)- and interferon gamma (IFN-gamma)-producing T cells (thus referred to as T helper type 1 [Th1] cells) are rendered unresponsive after in vivo administration of soluble HGG. In contrast, antigenic stimulation of T cells isolated from tolerant adult mice leads to increased production of IL-4 in vitro. In vivo challenge of dHGG-treated adult animals with hapten-coupled HGG (p-azophenylarsonate [ARS]-HGG) induced a significant ARS-specific antibody response, suggesting that tolerance induction in this model does not completely abrogate tolerogen-specific Th activity in vivo. In agreement with the in vitro data, hapten-specific antibody response of tolerant animals is characterized by a selective deficiency in the IFN-gamma-dependent IgG2a subclass. Injection of immunogenic forms of HGG into tolerant animals also produced an IL-4-dependent increase in total serum **IgE** levels, indicative of an increased activity of HGG-specific Th2 cells in these animals. The finding that tolerance induction differentially affects Th subpopulations suggests that crossregulation among lymphocyte subsets may play a role in the induction and/or maintenance of acquired tolerance in adults.

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